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The Journal of Allergy

VOL. 25 MARCH, 1954 NO. 2

Original Articles

INFLUENCE OF INOCULATION SITE UPON THE COURSE OF THE "ANAPHYLACTOID REACTION" TO DEXTRAN

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RATS given small doses of egg white, intravenously or intraperitoneally, develop an acute serous inflammation, selectively in certain "shock organs," namely, the paws, snout, ears and the clitoris or penis. This reaction is often preceded by cyanosis and usually accompanied by a pink arterial hyperemia, in the affected regions. Both clinically and histologically, the lesions so produced are reminiscent of the "allergic-anaphylactic type" of tissue response, but they require no preliminary sensitization by the evocative agent; hence they could not be designated as anaphylactic. The term "anaphylactoid reaction," or "anaphylactoid inflammation," used in the paper in which this type of response was first described,[1] is perhaps not entirely satisfactory. We shall nevertheless retain it here, as a provisional designation because, having been widely accepted, it came to be firmly associated in the literature with this particular type of hypersensitivity reaction. It is true that some workers preferred to call it "egg-white edema of the rat," but the reaction is not specific for egg white (it can also be elicited by dextran, globin, hyaluronidase, etc.), it is not a simple edema (histologically it corresponds to a serous inflammation) and, finally, it is not limited to the rat or even to the particular "shock organs" that respond in the rat (other species can react in the same manner and do so in different body regions).[2-4]

We became interested in the anaphylactoid reaction because it showed us that the course of a typical acute inflammation largely depends upon the functional activity of the adrenal cortex. It was found, for instance, that adrenalectomy sensitizes, while stimulation of the pituitary-adrenocortical axis (during the alarm reaction) desensitizes the rat to this anaphylactoid inflammation.[1, 5] Indeed, in December, 1944, when the concept of the "diseases of adaptation" was formulated,* the dependence of this response upon

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*In an address before the First Annual Meeting of the American Academy of Allergy, in December, 1944, subsequently published in this Journal.[6]

stress and corticoids furnished us with the first objective experimental proof of a close correlation between the general adaptation syndrome and hypersensitivity reactions.

Subsequently, it was demonstrated that ACTH and the antiphlogistic corticoids (cortisone, hydrocortisone) inhibit, while the somatotrophic hormone (STH) and the prophlogistic corticoids (e.g., desoxycorticosterone) aggravate the course of this type of inflammation.[7] The latter also proved to be highly sensitive to suppression by various antihistaminics.[5] Recently, it has been shown that substances capable of eliciting the anaphylactoid reaction can be produced endogenously by the tissue of Walker tumor transplants in the rat.[8] All these observations stimulated interest in this singular reaction and many workers are now using it as an indicator in investigations concerned with stress, adaptive hormones, antihistaminics, and tissue reactivity in general.

We shall not attempt to survey the voluminous pertinent literature in this communication, since several detailed reports on it have appeared elsewhere.[7, 9-12] However, as the test is widely used, we wish to call attention here to a new observation, which may not only explain some apparent inconsistencies in relevant publications, but perhaps even help to throw some light upon the mechanism through which this inflammation is produced. In brief, we found that the reaction depends largely upon the site at which the evocative material is introduced into the body. For instance, if an otherwise ineffective dose of a dextran solution is injected directly into a "shock organ" (e.g., a paw or the snout) inflammation ensues most readily, not only at the site of application, but even in distant "shock organs."

MATERIALS AND TECHNIQUES

Two hundred and eighty female albino Wistar rats, weighing 120 to 145 grams (average 133 grams) were subdivided into 28 equal groups. They were given a 6 per cent dextran solution ("Macrodex"), at various sites and in different amounts. For the sake of uniformity, all these injections were administered under slight ether anesthesia, since the intrajugular inoculation could not readily be performed otherwise. Preliminary control tests had shown us that light ether anesthesia during the introduction of dextran does not alter the response appreciably.

The anaphylactoid reaction was appraised separately, at the site of injection (topical response) and in distant "shock organs" (general response).

Readings were made one hour and two and one-half hours after injection and expressed in the following scale: 0 = no reaction; + = just noticeable definite reaction; ++ = intermediate reaction, and +++ = maximal reaction. In the case of injection into parts other than the "shock organs" (enumerated above), the topical response was never a characteristic anaphylactoid inflammation, but only a more or less marked edema. This was probably due to delayed absorption of the dextran solution, and we rated it

a "0" response. After intraperitoneal, intravenous and intrapleural injections, the topical response was not examined in this experimental series. However, we know from previous observations that the characteristic anaphylactoid reaction does not occur locally after the application of dextran at these sites.

The results of all our observations are summarized in Table I. Here, the mean of each reading is expressed by a figure corresponding to the sum of all plus signs in a group, divided by 10 (the number of animals).

TABLE I. INFLUENCE OF INOCULATION SITE UPON THE COURSE OF THE "ANAPHYLACTOID REACTION" TO DEXTRAN

GROUP	SITE OF DEXTRAN INJECTION	DOSE (ML.)	"ANAPHYLACTOID REACTION" AFTER 1 HOUR		AFTER 2½ HOURS	
			TOPICAL	GENERAL	TOPICAL	GENERAL
1	Intraperitoneal	0.3	—	2.8	—	2.0
2	Jugular (intravenous)	0.3	—	1.8	—	1.7
3	Intrapleural	0.3	—	1.7	—	2.5
4	Inguinal region (subcutaneous)	0.3	0	0	0	0
5	Lumbar region (subcutaneous)	0.3	0	0	0	0
6	Left hind paw (subcutaneous)	0.3	2.8	2.2	2.5	2.7
7	Left, above ankle (subcutaneous)	0.3	0	0	0	0
8	Right fore paw (subcutaneous)	0.3	2.9	1.1	2.6	2.7
9	Right, above wrist (subcutaneous)	0.3	0	0	0	0
10	Snout* (subcutaneous)	0.3	2.3	1.2	2.0	0.6
11	Parietal region (subcutaneous)	0.3	0	0	0	0
12	Intraperitoneal	0.2	—	0.5	—	2.2
13	Jugular (intravenous)	0.2	—	0.8	—	0.8
14	Lumbar region (subcutaneous)	0.2	0	0	0	0
15	Left hind paw (subcutaneous)	0.2	2.8	1.6	2.7	1.4
16	Left, above ankle (subcutaneous)	0.2	0	0	0	0
17	Snout* (subcutaneous)	0.2	2.3	0.7	1.7	0.1
18	Under chin (subcutaneous)	0.2	0	0	0	0
19	Intraperitoneal	0.1	—	1.0	—	3.0
20	Jugular (intravenous)	0.1	—	1.2	—	1.7
21	Left hind paw (subcutaneous)	0.1	2.8	1.6	2.8	1.5
22	Intraperitoneal	1.0	—	2.2	—	1.0
23	Jugular (intravenous)	1.0	—	0.4	—	0.3
24	Lumbar region (subcutaneous)	1.0	0	0	0	0
25	Intraperitoneal	3.0	—	1.8	—	1.2
26	Jugular (intravenous)	3.0	—	0.2	—	0.1
27	Lumbar region (subcutaneous)	3.0	0	0	0	0.2
28	Inguinal region (subcutaneous)	3.0	0	0.8	0	2.2

*Some of dextran solution lost through perforation into nasal or oral cavity.

In the case of the general reaction, a single reading represents the mean response of all the "shock organs" together, so as to express the topical and general reactions in comparable terms. For example, a topical response of 2.0 after dextran injection into the left hind paw, associated with the general response of 2.0 in the same animal, means that the swelling was of approximately the same intensity at the site of injection as in, say, the contralateral paw, the front paws, or the snout. It does not mean that the sum total of all the responses in distant "shock organs" amounted only to a mean of 2.0.

We did not follow the response longer than two and one-half hours, because after that, the swelling and hyperemia tend to subside and individual variations become quite considerable.

RESULTS

The first series of experiments, in which 0.3 ml. of dextran was injected (Groups 1 to 11) confirms our earlier finding that a given amount of anaphylactoid irritant is much more effective upon intraperitoneal or intravenous than after subcutaneous administration (for instance, in the inguinal or lumbar regions). These experiments also confirm the well-known fact that injection directly into a "shock organ" causes a particularly marked local response at the site of inoculation.

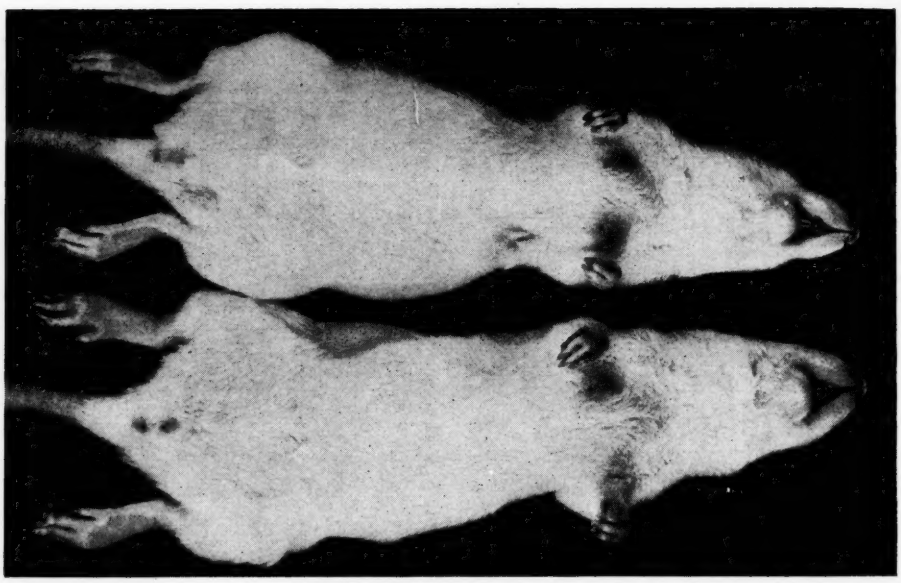

Fig. 1.—Production of a generalized anaphylactoid reaction by topical treatment of a "shock organ" with dextran. In the control rat (top) 0.3 ml. of dextran was injected just above the ankle of the left hind limb. The other rat received the same amount in the adjacent "shock organ" territory of the left hind paw. In the control, there is no anaphylactoid response. In the experimental animal, not only the injection site, but all other "shock organ" territories (the right hind paw, both front paws, the snout, and the clitoris) are swollen and hyperemic. In this (rather exceptional) case the general response was even more pronounced than the topical.

It is hardly unexpected that intrapleural injection of dextran is likewise highly effective, since the structure and function of the pleural lining is quite similar to that of the abdominal cavity.

It was rather surprising to note, however, that injection into the left hind paw (Group 6) caused a reaction of essentially the same magnitude in distant "shock organs" as at the site of application. This was considered to be all the more noteworthy since the same amount of the same dextran solution, given to comparable rats, a few millimeters above the ankle region of the left hind paw, caused neither a local nor a general reaction.

In comparing the local and distant responses, following injection into the right front paw (a "shock organ") and just above the right wrist (not a "shock organ") or to take an entirely different anatomic region, the snout

and the adjacent parietal region (cf. Groups 8 to 11), this close dependence of the response upon the inoculation site became even more obvious. Apparently if such a small amount of dextran is injected into any of the regions which would respond following systemic (e.g., intraperitoneal, intravenous, or intrapleural) administration, there is not only a rapid and intense topical response, but also a marked, though sometimes delayed, general reaction in distant "shock organs." If, on the other hand, the dextran is injected into the subcutaneous tissue elsewhere in the body, be it even at a distance of only a few millimeters from the "shock organs," there is neither a topical nor a general response.

These findings were confirmed by two additional series of observations, in which 0.2 ml. (Groups 12 to 18) or even 0.1 ml. of dextran (Groups 19 to 21) were similarly compared, after injection into different sites.

Groups 22 to 28 were added to examine the effects of massive doses of dextran, because some of our earlier observations with egg white showed that, after an optimal intravenous dose level is reached, the reaction tends to decline and in fact may be entirely absent. Since this phenomenon of self-inhibition has never been systematically explored, it was difficult to interpret the observations of some investigators, who obtained minimal anaphylactoid reactions with acute, shock-producing doses of intravenously administered dextran.[13]

The mechanism of this inhibition is not clear, but it is evident from our data that—at least after two and one-half hours, when the general reaction normally reaches its maximum—intraperitoneal injection of 1.0 ml. (Group 22) or 3.0 ml. (Group 25) of dextran is rather less effective than intraperitoneal administration of 0.3 ml. (Group 1), 0.2 ml. (Group 12), or even 0.1 ml. (Group 19). After one hour, this difference is less evident because the initial response, following intraperitoneal treatment with small volumes, tends to be slow and irregular in developing. This may be due to variations in absorption rate induced by differences in the peritoneal territory with which the dextran happens to come into contact.

Following intravenous administration of 1.0 and particularly of 3.0 ml., the rat immediately becomes intensely cyanotic and may show signs of impeded breathing. However, it recovers from this shocklike condition within a few minutes and, after that, rarely shows any significant amount of general anaphylactoid reaction (Groups 23 and 26). Smaller intravenous doses are usually more efficacious in producing a general anaphylactoid response (Groups 2, 13, 20) but we did not obtain a near maximal reaction at any of the dosage levels studied when the dextran was introduced directly into the jugular vein.

DISCUSSION

It is evident that when dextran is injected directly into one of the specially responsive regions of the rat ("shock organs"), not only the topical, but even the distant anaphylactoid reaction is especially pronounced.

Marked general effects in the "shock organs" also can be obtained following the intravenous, intraperitoneal, and intrapleural injections of dextran, although here, the site of administration does not react with a typical anaphylactoid inflammation.

It is possible that the absorption of dextran occurs at the most favorable rate when the substance is directly injected into a "shock organ" or one of the large serous cavities. Yet, even direct injection into the blood, or into the large serous cavities, does not evoke a more pronounced general response than that obtained following topical injection of the same dose into one of the "shock organs." It is also noteworthy that injection of dextran into the tissue immediately adjacent to the "shock organ" is virtually ineffective.

The possibility must be considered that some product of the reaction between dextran and the tissues of the "shock organs" is the immediate cause of the anaphylactoid reaction in distant regions, but we have no direct evidence to show that this is the case.

When dextran is administered subcutaneously at a distance from the "shock organs," it does not tend to produce any anaphylactoid inflammation, either topically or in the "shock organs," except when enormous amounts are administered. Among the subcutaneous injection sites outside the specially responsive areas, the inguinal region proved to be by far the best suited for the production of this response.

It is not our intention to enter into a lengthy discussion of the various possible interpretations of our findings at this time. Suffice it meanwhile merely to point out that this reaction, which is now widely used for various studies on hypersensitivity, is greatly dependent upon the site at which the eliciting agent is introduced into the body.

SUMMARY

The so-called "anaphylactoid reaction" is an acute serous inflammation limited to certain "shock organs," namely, the paws, ears, snout, and the clitoris or penis. It is readily elicited by the intravenous, intraperitoneal or intrapleural injection of small doses of dextran.

Small amounts of dextran, injected subcutaneously into such susceptible regions as the front or hind paws and the snout, produce not only a very marked topical inflammation but also a pronounced response in distant "shock organs." In fact, under these conditions, even the hypersensitive regions, remote from the injection site, react more markedly than if the same amount is directly injected into the blood.

Administration of comparable quantities of dextran into the subcutaneous tissue anywhere in the immediate vicinity, but just outside a "shock organ," does not evoke either a local or a distant anaphylactoid response.

In the event of direct intravenous administration of dextran, a maximal response is obtained at a relatively low dosage level; as the dose is raised above this, activity declines.

It is not yet evident why dextran, injected directly into a region where it can produce topical anaphylactoid inflammation, also elicits a similar response at a distance, but certain possible pathogenic mechanisms have been considered.

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THE ROLE OF EPINEPHRINE AND THE EFFECT OF AMINE OXIDASE INHIBITOR (MARSILID) IN ANAPHYLAXIS IN THE GUINEA PIG

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THE protective role of epinephrine in anaphylaxis and related conditions has been studied quite extensively.[1-5] Although the degree and mode of its action are not completely settled, in general, the effects may be ascribed to two classes of action, pharmacologic and hormonic.

Some of the pharmacologic actions of epinephrine seem to depend on the technique of the experimentation, especially on the size of the dose administered and the time relationship of its administration. The results have consequently varied with different investigators. The sympathomimetic action of epinephrine, described by Elliott in 1905 and considered by most investigators to be important in shock, is not entirely recognized by Danielopolou.[6] The latter believes that the action is "amphomimetic" depending upon the size of the applied dose, small doses producing a compensatory parasympathomimetic effect. Haag and associates[7] found a greater mortality in sensitized guinea pigs pretreated by repeated injections of epinephrine as compared to a control group which did not receive epinephrine. However, Hajós[8] was successful in preventing anaphylactic death in sensitized guinea pigs by the intravenous administration of epinephrine 15 minutes before challenge.

The fate of epinephrine in vivo is still obscure and the knowledge of its inactivation in vitro can also be considered far from complete. Gaddum and Kwiatkowski[9] concluded that epinephrine is oxidized in vivo by amine oxidase. Richter and Tingley[10] stressed the fact that the rate of oxidation by amine oxidase is probably too slow to account for the speed with which epinephrine is inactivated in vivo. Although other pathways of epinephrine inactivation have been suggested, it is conceded that inactivation by amine oxidase is the major mechanism, being responsible for about 50 per cent of the degradation.

Amine oxidase can be inhibited by a number of amines with a high affinity for this enzyme, such as mono- and diguanidines, mono- and diamidines, and other substances. Zeller and associates[11, 12] described an almost complete inhibition of amine oxidase activity in rats and guinea pigs, both in vitro and

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in vivo by the subcutaneous injection of 1-isonicotinyl-2-isopropyl hydrazine (Marsilid). Previous to Marsilid no single drug was known which completely inhibited amine oxidase both in vitro and in vivo. As a result of these observations, it semed of interest to investigate the effect of this drug in inhibiting the acton of amine oxidase especially with respect to the in vivo metabolism of endogenous and exogenous epinephrine.

The purpose of this paper is to present observations on (a) the effect of epinephrine administration on anaphylaxis in guinea pigs with respect to time relationship and quantitative factors and (b) the effect of the administration of 1-isonicotinyl-2-isopropyl hydrazine on the anaphylactic manifestations in guinea pigs.

PROCEDURE

The effect of a single subcutaneous dose of epinephrine was compared with an infusion of the drug on the anaphylactic symptoms in the guinea pig. Animals were sensitized passively by the intracardial injection of 1 ml./kg. body weight of guinea pig antiovalbumin serum. Forty-eight hours later they were challenged by exposure to an aerosol obtained from a 0.2 per cent solution of twice crystallized ovalbumin, as described by Feinberg and Malkiel.[13] Sensitized animals, not receiving epinephrine, respond with asthma under these conditions in about one to two minutes. Significant retardation of time of response indicates a protective effect. Other groups of animals were sensitized actively by injecting 10 mg. of twice crystallized ovalbumin intraperitoneally. These animals were challenged 13 days later by an intracardial or intravenous injection of 10 to 15 mg. of ovalbumin in solution. The degree of anaphylaxis and incidence of anaphylactic death were noted in the controls and compared with epinephrine-treated animals.

The single dose of epinephrine varied from 0.05 to 0.5 ml. of a 1:1,000 solution. The infusions consisted of amounts varying from 0.1 to 2 ml. of epinephrine administered in 125 ml. of physiologic saline by continuous subcutaneous clysis for one hour before challenge. Because of the marked amount of fluid which accumulated in a small area causing delayed absorption and local necrosis, 190 T. U. hyaluronidase were added to the infusions. This enzyme did not influence the course of the anaphylactic response.

The effect of Marsilid on epinephrine action was investigated by administering the drug to actively and passively sensitized animals. The possible effect of Marsilid was thus noted on the endogenous epinephrine. Other groups received epinephrine in single subcutaneous doses or by infusion. The dose of Marsilid was 50 mg./kg., 2 to 6 hours before antigen challenge.

The epinephrine used in this investigation was the commercial Parke, Davis Adrenalin Chloride Solution 1:1,000. The 1-isonicotinyl-2-isopropyl hydrazine (Iproniazid) was the commercial product of Hoffmann-La Roche Marsilid Phosphate. The hyaluronidase was Wyeth's Wydase. No sterility precautions were observed in the experiments. Guinea pigs of both sexes of different ages and weights were used.

RESULTS

I. *Effect of Single Doses of Epinephrine in Prevention of Anaphylaxis.—*

Asthma from antigen aerosol: Group 1. As can be seen in Table I thirteen animals receiving single subcutaneous injections of epinephrine showed a much milder reaction to the antigen aerosol than the six controls not protected by epinephrine. The exposure time producing a reaction was considerably longer in the epinephrine-treated group. Larger doses seemed to give better protection.

TABLE I

	NO. ANIMALS	EPINEPHRINE HYPO. ML.	EPINEPHRINE INFUSION ML.	TIME BEFORE CHALLENGE	MARSILID HOURS BEFORE CHALLENGE	AVERAGE TIME REQUIRED BEFORE REACTION RATIO DEAD/TOTAL 3+	2+	1+	0
ASTHMA FROM AEROSOL									
Group 1. Epinephrine	2	0.05		15′			5′35″		
	2	0.1		15′				10′	
	4	0.15		15′			5′15″		
	1	0.2		60′ and 30′				9′10″	
	1	0.2		30′				10′	
	3	0.2		60′ and 15′				8′40″	
Controls	6					3′36″			
Group 3. Epinephrine	11		1.0	60′					10′
*Controls	4					3′35″			
Group 5. Marsilid	10				2		2′18″		
Group 7. Marsilid	6	0.15		15′	2		5′50″		
ANAPHYLACTIC SHOCK									
						RATIO DEAD/TOTAL			
Group 2. Epinephrine	5	0.5		15′			1/5		
Controls	3						3/3		
Group 4. Epinephrine	4		0.1	60′			3/4		
	10		0.4	60′			3/10		
	4		0.5	60′			0/4		
	5		0.6	60′			1/5		
Controls	20						11/20		
Group 6. Marsilid	4				6		3/4		
†Controls	6						3/6		
Group 8. Marsilid	5	0.05			2		3/5		
Group 9. Marsilid	8		0.4	60′	2		7/8		

*Controls for groups 3, 5, and 7.
†Controls for groups 6, 8, and 9.

Anaphylactic shock: Group 2. Five out of the eight actively sensitized animals were challenged with intracardial or intravenous injections. A single injection of 0.5 ml. epinephrine was administered 15 minutes before challenge.

One of the guinea pigs died immediately after epinephrine administration before it could be challenged. This death was ascribed to the toxic action of the drug. Another of the animals died in anaphylaxis. Three seemed to be protected. All three controls had severe symptoms and two of them died.

II. *Effect of Infusion of Epinephrine on the Prevention of Anaphylaxis.—*

Asthma from antigen aerosol: Group 3. Eight guinea pigs pretreated

with 1 ml. and three with 2 ml. of epinephrine administered in 125 ml. of physiologic saline by continuous subcutaneous clysis showed a complete protection when subjected to ovalbumin aerosol. The animals were in the chamber for 70 minutes, while each of the four controls developed a reaction in less than 10 minutes. In all subsequent infusion experiments Wydase was added to the infusion.

Anaphylactic shock: Group 4. Twenty-three actively sensitized animals were given varying doses of epinephrine by infusion prior to intravenous or intracardial challenge with the antigen. Of four which were given 0.1 ml. of epinephrine, three died and one showed a 4+ reaction. Of the 10 receiving 0.4 ml. of the drug three died, four developed a 1+ to 2+ reaction and the remainder showed complete protection. None of the four animals receiving 0.5 ml. epinephrine showed any anaphylactic symptoms. Of the five guinea pigs receiving 0.6 ml. epinephrine one died, and the others were completely protected. Of the twenty controls not receiving epinephrine, eleven died in anaphylaxis, five developed a 4+ reaction, three a 3+, and one a 2+ reaction.

III. *Effect of Marsilid on Anaphylaxis.*—

Animals not treated with epinephrine: Group 5. Each of the ten animals in this group received intraperitoneal injections of Marsilid phosphate, 50 mg./kg., 2 hours before exposure to the 0.2 per cent ovalbumin aerosol. None of them were protected in that the average exposure time was 2 min., 12 sec., as compared to an average of 2 min., 30 sec., for the control group.

Group 6. Three out of the four guinea pigs treated with Marsilid, 50 mg./kg., intraperitoneally, 6 hours previously died after challenge by intracardial injections of antigen. The fourth developed a 4+ reaction. Of the six controls three died and three developed a 4+ reaction.

Animals given a single injection of epinephrine: Group 7. The reactions of the six guinea pigs challenged by aerosolized antigen 2 hours after receiving Marsilid, 50 mg./kg. intraperitoneally, and 15 minutes after subcutaneous injections of 0.15 ml. of epinephrine were of about the same character and degree as those produced in the guinea pigs of Group 1 which received 0.15 ml. of epinephrine 15 minutes before challenge. This reaction consisted of a mild dyspnea occurring after an exposure of an average time of 5 minutes. All ten animals in both groups were able to stay in the chamber longer than 10 minutes.

Group 8. Three of the five animals which received 50 mg./kg. of Marsilid intraperitoneally 2 hours before and 0.05 ml. of epinephrine subcutaneously 15 minutes before challenge by single injections died in anaphylaxis, one developed a 1+ and another 3+ reactions.

Animals given an infusion of epinephrine: Group 9. Eight guinea pigs used in this experiment were given 0.4 ml. of epinephrine by infusion preceded by the administration of 50 mg./kg. Marsilid two hours earlier. Seven animals died and one developed a 4+ reaction.

All animals receiving epinephrine by a continuous drip showed a tachypnea occasionally difficult to differentiate from the dyspnea of the anaphylactic reaction. In all seven animals which received Marsilid in addition to epinephrine blood was found in the thoracic cavity although there was no evidence of cardiac tamponade or other serious injury. In only two of the seven animals which did not receive Marsilid and which died from anaphylaxis were there comparable findings.

DISCUSSION

The results of these experiments seem to indicate that not only does epinephrine in small doses (up to 0.05 ml. of a 1:1,000 dilution) fail to protect shocked animals, but also that the anaphylactic reaction appears sooner than in the controls. These results apparently corroborate Danielopolou's claims. The findings of Haag and associates[7] that a greater mortality results in shocked guinea pigs pretreated by repeated injections of small, nonprotective doses of epinephrine might be accounted for by a possible deleterious effect from the prolonged administration of the drug. It is quite possible also that epinephrine in small doses fails to give protection not only because of a compensatory parasympathomimetic mechanism, but also because it might act as a liberator of "free" histamine as do the antihistamines.[14] Thus, Eichler and Barfuss[15] and Staub[16] noted an increase in the plasma histamine during and after epinephrine infusion. Basing their conclusions on the observations of others, Yonkman and associates[17] attempt to explain epinephrine fastness following intravenous administration of this drug on the release of histamine. On the other hand the important observation made by Werle[18] that epinephrine inhibits 1-histidin decarboxylase suggests that this hormone may block histaminogenesis at the cell level.

In addition, several other mechanisms have been suggested to account for the protective effect of epinephrine. It has been postulated[6, 19] that the protective effect of epinephrine is due to its direct action upon the cells of end organs. One may hypothesize that endogenous epinephrine is involved in the interference with carbohydrate metabolism which has been observed experimentally[20, 21] and clinically[22-24] in anaphylaxis. It is unlikely that the protective role of epinephrine in anaphylaxis is due to its action on the hypothalamus-pituitary-adrenal axis, for the effect of epinephrine is relatively more rapid than one expects from ACTH or cortisone. Furthermore, unlike the case of epinephrine, neither of the last two hormones protects the animals in anaphylactic shock.[25, 26] According to some recent investigations[27] epinephrine does not play as important a part in the production of increased pituitary adrenocorticotropic activity as others have believed.

Trendelenburg[28] has recognized that the action of epinephrine depends upon the concentration of the drug. The manner of administration also seems to be of importance. Based on their electrocardiographic findings, Ikonomou and Lindner[29] showed that as a result of preliminary small infusions of epinephrine a greater tolerance for subsequent toxic doses developed in guinea pigs.

When too large doses of epinephrine (0.5 to 0.6 ml.) were administered by single injection the animals died, probably due to the toxicity of the drug. These doses seemed to give protection to the challenged animals before death in that typical symptoms of anaphylaxis were not manifested. When given by a continuous drip the effective dose seemed to be proportional to the concentration (over a range 0.4 to 2.0 ml.). A dose given in a single injection which seemed to be on the borderline of tolerance was easily tolerated in continuous infusion.

The administration of Marsilid or its addition to epinephrine not only failed to produce protection of the shocked animals but also appeared to have an injurious effect on them: more blood extravasations were noted in animals pretreated with Marsilid than in those not pretreated. Similar observations have been made clinically.[30] The undesired side effects of this drug can be explained not only by its toxicity, but possibly also by the inhibition of the diamine oxidase (Zeller and associates[11]) which is responsible for the breakdown of histamine.

Another enzymatic breakdown of histamine was found recently by Zeller[31] which is even more strongly inhibited by Marsilid than is diamine oxidase (histaminase). It is quite possible that the inhibition of this new pathway of histamine breakdown may play an important role in reversing the enzymatic balance after inhibition of amine oxidase. It is important to stress that the inhibition of amine oxidase would give only minor results if there existed a second major mechanism for epinephrine degradation. Richter[32] came to the conclusion that the main physiologic process by which epinephrine is inactivated in the body is by conjugation. The results of Schayer[33a, 33b] based on studies with β-C^{14}-epinephrine indicate the presence of at least five radioactive substances in the urine of rats given this epinephrine. He postulates that there are at least two pathways in the breakdown of epinephrine.[33b, 33c] However, there are many ways of inactivating this hormone, depending upon the site of oxidation, the side chain, or the ring structure of the molecule. Also, there are enzymes in addition to amine oxidase which play an important role in epinephrine inactivation. While Marsilid is blocking the amine oxidase, these may still be active.

SUMMARY

1. Epinephrine protects guinea pigs in anaphylactic shock when administered in optimal doses.

2. Protective doses of epinephrine administered by continuous infusion seem to be less dangerous and more efficacious than when given in single injections.

3. l-isonicotinyl-2-isopropyl hydrazine (Marsilid) is without any protective effect on anaphylactic shock or asthma from an aerosolized antigen in guinea pigs.

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ORAL HYDROCORTISONE THERAPY IN BRONCHIAL ASTHMA AND HAY FEVER

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THE use of oral cortisone in the symptomatic relief of bronchial asthma[1, 2] and hay fever[3] has previously been reported from our clinic. It has been noted and amply confirmed by other workers[4-10] that the degree and persistence of relief in the treatment of bronchial asthma with intramuscular cortisone, and oral cortisone in hay fever, were outstanding. Relief persists during the period of therapy and for variable periods following the discontinuation of treatment. With most patients, the symptoms return within several hours to two weeks after therapy with cortisone is discontinued. Nevertheless, the remarkable symptomatic relief which is obtained cannot be ignored, and, though usually restricted to the period in which therapy is employed, offers a very effective mode of therapy.

SCOPE OF STUDY

In this study, an evaluation of oral therapy with hydrocortisone* (free alcohol) in the treatment of bronchial asthma and hay fever was undertaken. A total of 49 patients were included in the investigation, 39 suffering from bronchial asthma and 10 from hay fever.

Although the patients had experienced varying degrees of relief in previous years with the methods of therapy then available, the therapeutic results with hydrocortisone were almost invariably more gratifying than had hitherto been obtained. Except for oral therapy with hydrocortisone, no other form of anti-allergic treatment was given during this study.

DOSAGE SCHEDULE

The objective of therapy was the daily administration of the smallest oral dose which would maintain the greatest amount of symptomatic relief. This naturally varied from patient to patient, the exact dosage for each case included in this study being presented in Tables I, II, and III. In general, therapy was initiated with a daily dose of 80 mg. and rapidly reduced to a maintenance dosage of 40 to 60 mg. daily. The daily dose was administered in four divided doses, with each meal and at bedtime. Occasionally the dosage was so divided that a somewhat larger individual dose was administered at bedtime than was administered after each meal.

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RESULTS OF THERAPY

In the dosage described for each of the patients with asthma, oral hydrocortisone (free alcohol) generally produced striking relief of symptoms. There was excellent relief of all symptoms in 20, marked relief in 5, moderate relief in 9, and slight relief in one. Four patients in this group failed to respond to treatment.

In the series of 39 asthmatic patients treated with hydrocortisone, 24 had previously been treated with adequate doses of cortisone. Of these 24 patients, 15 derived the same benefit with hydrocortisone that was previously obtained with cortisone. Six of the patients who obtained only partial relief with cortisone subsequently obtained greater relief from the oral administration of hydrocortisone. Two patients were not relieved previously with cortisone and obtained excellent relief with hydrocortisone. Significantly, no patient who was treated with both cortisone and hydrocortisone obtained any greater relief from the use of cortisone than was obtained from hydrocortisone. As mentioned previously, 8 patients obtained better relief from hydrocortisone than they had previously obtained from the use of cortisone. One of the 4 patients who failed to respond to hydrocortisone had also failed to respond to cortisone; the other 3 patients who failed to respond to hydrocortisone had not previously received cortisone (Table II).

Of 10 patients with severe hay fever treated with oral hydrocortisone, excellent relief was obtained in 7, marked relief in 2, and moderate relief in one (Table III).

DISCUSSION

Although not curative by any means, as is also the case with the use of cortisone, the treatment of bronchial asthma and hay fever with oral hydrocortisone (free alcohol) is nevertheless so gratifying that its use in individuals who cannot be otherwise controlled is both feasible and justified. Therapy with hydrocortisone is indicated in those patients in whom symptoms persist after the application of the usual therapeutic measures, such as hyposensitization, antihistamines, bronchodilators, etc., and in whom none of the contraindications to the use of cortisone or hydrocortisone exist.

By reducing the daily dosage to the point necessary to maintain the maximum degree of symptomatic relief, both the side effects and the cost associated with the prolonged use of hydrocortisone are minimized.

Side effects were encountered in 9 of the entire series of 49 patients, but were sufficiently significant in only two (No. 18, Table I and No. 10, Table III), as to require discontinuation of therapy. All side effects that might have conceivably been due to actual therapy with hydrocortisone are listed in Table I and Table III.

Of the 39 patients with bronchial asthma treated with hydrocortisone, 24 had previously been treated with cortisone. The incidence and degree of severity of side effects were similar with both drugs. The patients who experienced side

TABLE I. RESULTS OF ORAL HYDROCORTISONE THERAPY IN BRONCHIAL ASTHMA

CASE NO.	PATIENT	AGE	SEX	DURATION OF ASTHMA	DAILY DOSE (MG.)		DAYS OF THERAPY	RESULTS	RELIEF		SIDE REACTIONS	COMMENTS
					INITIAL	MAINTENANCE			BEGAN (DAYS)	LASTED (DAYS)		
1.	H. F.	36	F.	22 yr.	100	60-80	354	3 plus	1	354	Weight gain 5 lb.	21 mo. of previous cortisone therapy increased weight by 28 lb.; marked relief with cortisone
2.	E. L.	28	M.	14 mo.	100	60-80	26	0	--	--	Weakness, sweating	No relief with ACTH or cortisone
3.	M. D.	47	F.	12 yr.	80	60	62	1 plus	3	60	Sweating, abdominal cramps	Slight relief with ACTH and cortisone; cortisone side effect—sweating
4.	P. F.	45	M.	7 yr.	80	60-80	14	0	--	--	None	Bronchial asthma, rheumatic heart disease, and congestive heart failure
5.	E. M.	50	M.	33 yr.	100	40-60	17	4 plus	1-2	29	None	Excellent relief with cortisone
6.	G. L.	47	M.	4 yr.	80	40	410	4 plus	3	408	Weight gain 15 lb.	No relief with ACTH or cortisone
7.	L. N.	21	M.	15 yr.	80	80	4	4 plus	1	150	None	Cortisone—excellent relief
8.	M. W.	50	F.	14 mo.	80	60-80	39	4 plus	1	43	None	Cortisone—excellent relief
9.	P. H.	42	M.	4 yr.	80	60	26	4 plus	1	28	Epigastric fullness	Cortisone—moderate relief
10.	R. D.	19	M.	18 yr.	80	60	124	2 plus	2	123	None	Cortisone—moderate relief
11.	H. B.	40	F.	22 yr.	80	20-60	180	3 plus	1-2	178	Fullness of face	Cortisone—moderate relief; ACTH—moderate relief
12.	H. S.	32	M.	15 yr.	100	80-100	48	2 plus	3	46	None	Cortisone—moderate relief; ACTH—moderate relief
13.	F. F.	37	F.	4 yr.	60	60	7	4 plus	1	90	None	Cortisone—moderate relief; hydrocortisone, relief excellent and more rapid
14.	H. D.	44	F.	8 yr.	80	60	152	2 plus	2	151	None	ACTH—marked relief; cortisone—slight relief
15.	G. L.	32	M.	29 yr.	80	60	8	4 plus	2	70	None	Complete relief with hydrocortisone in 72 hr.
16.	I. E.	38	M.	12 yr.	80	60	7	4 plus	1	90	None	Relief in 5 hr. with hydrocortisone
17.	W. C.	15	M.	11 yr.	60	40-60	64	2 plus	1	63	None	
18.	S. T.	37	F.	7 mo.	60	40-60	17	2 plus	1	16	Sweating, tachycardia, dizziness	Medication discontinued because of side effects
19.	L. P.	55	M.	3 yr.	80	20-60	14	4 plus	4-5	32	None	Cortisone—excellent relief
20.	D. B.	12	F.	7 yr.	20	20	6	4 plus	1	19	None	Complete relief in 4 hr. with hydrocortisone

TABLE I—CONT'D

TABLE I—CONT'D

21.	A. M.	58	M.	27 yr.	80	60	82	2 plus	2-3	80	None	Cortisone—moderate relief
22.	C. N.	44	M.	2 yr.	80	60	16	4 plus	2	21	None	
23.	N. P.	22	M.	12 yr.	60	60	2	4 plus	1	36+	None	Complete relief in 24 hr.; cortisone—excellent relief
24.	T. F.	46	F.	8 yr.	80	40-60	35	4 plus	2	48+	None	ACTH and cortisone gave excellent symptomatic relief but chest not clear; chest clear for first time in 12 mo. on hydrocortisone
25.	J. S.	62	M.	35 yr.	60	60	34	4 plus	1	33	None	Marked symptomatic relief in 24 hr.; chest clear for first time after 33 days of hydrocortisone
26.	A. C.	32	M.	3 yr.	80	40-80	35	4 plus	1-2	34	None	Cortisone—excellent relief
27.	B. K.	52	M.	20 yr.	80	60-80	26	2 plus	3-4	23	None	Slightly better relief than with cortisone or ACTH
28.	J. H.	32	F.	22 yr.	80	80	21	3 plus	1-2	20	None	Cortisone—marked relief
29.	D. R.	25	M.	2 yr.	80	40-60	29	3 plus	2	28	None	Cortisone—slight relief; no increase in previous episodes of epistaxis with hydrocortisone
30.	I. N.	48	M.	6 yr.	40	40	22	4 plus	1-2	21	None	ACTH—no relief; cortisone—no relief
31.	K. W.	50	F.	4 yr.	80	60-80	42	2 plus	2	40	None	Cortisone—moderate relief
32.	R. N.	47	F.	23 yr.	80	60	6	3 plus	1-2	6+	None	No recurrence of previous psychosis during or after hydrocortisone
33.	M. B.	70	M.	6 yr.	80	60	4	0	0	0	None	No relief with bronchodilators previous to hydrocortisone; relief following hydrocortisone
34.	P. U.	53	F.	3 yr.	80	60	14	2 plus	1-2	13	None	
35.	S. B.	25	M.	10 yr.	60	60	3	0	0	0	None	ACTH—no relief; relief with hospitalization, bronchodilators, and antibiotics
36.	D. G.	26	F.	1 yr.	60	60	12	4 plus	1-2	11	None	
37.	I. A.	33	M.	3 mo.	40	40	23	4 plus	1-2	31	None	
38.	H. G.	5	F.	3 yr.	20	20	7	4 plus	1	53+	None	Excellent relief with daily dose of 20 mg. of hydrocortisone
39.	N. L.	23	F.	21 yr.	60	60	7	4 plus	1-2	82+	None	

4 plus, excellent relief of symptoms.
3 plus, marked relief of symptoms.
2 plus, moderate relief of symptoms.
1 plus, slight relief of symptoms.
0, no relief.

TABLE II. COMPARATIVE STUDIES OF THE TREATMENT OF BRONCHIAL ASTHMA WITH ORAL CORTISONE AND ORAL HYDROCORTISONE

	CORTISONE				HYDROCORTISONE			
	DAILY DOSE (MG.)		DEGREE OF		DAILY DOSE (MG.)		DEGREE OF	
CASE NO.	INITIAL	MAINTENANCE	RELIEF	SIDE EFFECTS	INITIAL	MAINTENANCE	RELIEF	SIDE EFFECTS
1. (H. F.)	300	100-150	3 plus	Weight gain	100	60-80	3 plus	Weight gain
2. (E. L.)	100	100	0	Weakness, sweating	100	60-80	0	Weakness, sweating
3. (M. D.)	150	100-150	1 plus	Sweating	80	60	1 plus	Sweating, abdominal cramps
5. (E. M.)	100	50-100	4 plus	None	100	40-60	4 plus	None
6. (G. L.)	300	100	0	Weight gain	80	40	4 plus	Weight gain
7. (L. N.)	100	100	4 plus	None	80	80	4 plus	None
8. (M. W.)	100	75-100	4 plus	None	80	60-80	4 plus	None
9. (P. H.)	100	100	2 plus	Epigastric fullness	80	60	4 plus	Epigastric fullness
10. (R. D.)	100	100	2 plus	None	80	60	2 plus	None
11. (H. B.)	100	50-75	2 plus	Fullness of face	80	20-60	3 plus	Fullness of face
12. (H. S.)	100	100	2 plus	None	100	80-100	2 plus	None
13. (F. F.)	100	75	2 plus	None	60	60	4 plus	None
14. (H. D.)	100	100	1 plus	None	80	60	2 plus	None
19. (L. P.)	100	25-75	4 plus	None	80	20-60	4 plus	None
21. (A. M.)	100	50-100	2 plus	None	80	60	2 plus	None
23. (N. P.)	100	75-100	4 plus	None	60	60	4 plus	None
24. (T. F.)	100	100	4 plus	None	80	40-60	4 plus	None
26. (A. C.)	100	100	4 plus	None	80	40-60	4 plus	None
27. (B. K.)	100	100	2 plus	None	80	60-80	2 plus	None
28. (J. H.)	100	100-150	2 plus	None	80	80	3 plus	None
29. (D. R.)	150	100	1 plus	None	80	40-60	3 plus	None
30. (I. N.)	100	100	0	None	40	40	4 plus	None
31. (K. W.)	100	100	2 plus	None	80	60-80	2 plus	None
37. (I. A.)	100	75	4 plus	None	40	40	4 plus	None

TABLE III. RESULTS OF ORAL HYDROCORTISONE THERAPY IN RAGWEED HAY FEVER

PATIENT	AGE	SEX	PREVIOUS TREATMENT RAGWEED INJ.	DAILY DOSE (MG.) INITIAL	DAILY DOSE (MG.) MAINTENANCE	DAYS OF THERAPY	RESULTS	SIDE REACTIONS	COMMENTS
1. J. H.	56	M.	13 yr.	80	60	13	4 plus	None	Desensitization to ragweed for 13 yr. combined with antihistamines for 8 yr. with no relief; best season since 1917
2. N. L.	23	F.	9 yr.	80	40-60	14	4 plus	None	Desensitization to ragweed for 9 yr., antihistamines for 8 yr. gave no relief; complete relief in 24 hr. with hydrocortisone
3. E. F.	25	M.	9 yr.	80	40-60	14	4 plus	Acne	Complete relief with hydrocortisone in 9 hr.; acne cleared in 3 wk. after discontinuation of hydrocortisone
4. M. N.	52	F.	14 yr.	60	60	12	4 plus	None	Marked relief in 5 hr.; complete relief in 24 hr.
5. F. E.	48	F.	13 yr.	60	60	2	2 plus	None	Desensitization 13 yr. and antihistamines 7 yr. gave fair to good relief; only slightly better relief with hydrocortisone
6. F. T.	28	F.	1 yr.	60	40-60	8	4 plus	None	Symptoms very severe; 250 tissues each day previous to hydrocortisone; complete relief in 24 hr.
7. F. P.	36	F.	1 yr.	60	60	3	3 plus	None	Moderate relief with desensitization and antihistamines alone
8. M. F.	16	M.	8 yr.	60	40	2	3 plus	None	Marked relief in 12 hr.; duration of hydrocortisone, 2 days; duration of remission—no recurrence of symptoms for remainder of season
9. A. S.	14	M.	None	60	40-60	7	4 plus	None	Marked relief in 45 minutes after initial dose of 20 mg.; complete relief in 12 hr.
10. M. B.	18	M.	6 yr.	60	60	4	4 plus	Headache	Hydrocortisone discontinued because of headache on fourth day; duration of remission, 7 days

4 plus, excellent relief of symptoms.
3 plus, marked relief of symptoms.
2 plus, moderate relief of symptoms.
1 plus, slight relief of symptoms.
0, no relief.

effects with one drug also experienced similar side effects with the other. It was also noted that any patient who was able to tolerate cortisone without side effects also tolerated hydrocortisone.

Since the use of hydrocortisone in bronchial asthma and hay fever requires short-term therapy in most cases, extensive laboratory tests are unnecessary, since significant side effects are not to be expected. The patient's weight serves as an excellent guide to water and salt retention. The possibility of glycosuria may be checked by periodic examination of the urine. A low sodium diet, supplemental oral administration of potassium chloride, and periodic blood chemistry examinations are desirable when therapy is continued for any length of time. There need be no hesitancy about gradually reducing the daily dosage. When that dose becomes inadequate, prompt remission of symptoms will follow restoration of a higher daily dose for a few days.

SUMMARY

Thirty-nine patients with bronchial asthma and 10 patients with ragweed hay fever were treated with oral hydrocortisone tablets.

Of the 39 asthmatic patients, 20 obtained excellent relief of symptoms; 5, marked relief; 9, moderate relief; and 1, slight relief. Four patients failed to respond. Of the 10 ragweed hay fever patients, 7 obtained excellent relief; 2, marked relief; and 1, moderate relief.

Where cortisone had previously been used (24 patients) the response to hydrocortisone orally was as effective in 15, and superior in 8 patients. One patient failed to respond to both cortisone and hydrocortisone.

Significant side effects requiring discontinuation of therapy were observed in two patients, consisting of headache in one, and sweating, tachycardia, and dizziness in the other. Mild side effects were present in 7 patients. Forty patients showed no side effects. No serious side effects were encountered in this series.

Oral hydrocortisone is an effective form of therapy for symptomatic relief in bronchial asthma and hay fever.

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STUDIES ON THE SENSITIVITY OF MICE TO HISTAMINE FOLLOWING INJECTION OF HEMOPHILUS PERTUSSIS

II. Effect of Various Substances Upon Histamine Hypersensitivity

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IN 1948 Parfentjev and Goodline[1] made the interesting observation that mice injected with *Hemophilus pertussis* phase I cells become markedly sensitive to histamine within four days after the injection of the cells. This observation has been since confirmed and expanded by various workers.[2-10]

During a period of many months in which numerous experiments have been performed in our laboratories with pertussis-vaccinated mice, it has been noticed that a small percentage of these mice are able to survive large doses of histamine while smaller doses of the drug produce a higher death rate. This phenomenon is not marked and in some individual experiments is hardly significant. In searching for substances that would inhibit the development of this histamine sensitivity produced in mice by *H. pertussis*, it has been noticed that propylene glycol, a substance used as a diluent for the various compounds under test, was capable of protecting pertussis-sensitized mice against large doses of histamine but not against smaller amounts of the same drug. This effect of propylene glycol was so striking that it was decided to determine whether this protection was specific for propylene glycol or whether it was generally produced by many substances of varied nature. With this in mind a number of compounds have been tested for their effect on the histamine sensitivity of pertussis-vaccinated mice.

EXPERIMENTAL RESULTS

Mice injected with 1-2 billion *H. pertussis* cells show a tendency to resist to a greater degree higher doses of histamine than lower doses of the same drug. Fig. 1 gives the accumulated results of 23 separate experiments in which Tumblebrook Farm (TF) female mice weighing 14 to 16 Gm. each were injected intraperitoneally with 1 or 2 billion cells and four days later challenged intraperitoneally with graded doses of histamine. It is clear from this graph that although mice become highly sensitive to low doses of histamine (0.5 to 2 mg.) there is a greater survival of mice injected with higher doses of the drug (8 mg.). This survival at the high dosage of histamine is admittedly small in the immunized mice and not present in normal mice even

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when the amounts of histamine are increased to 96 mg. of histamine per mouse.[11] It should also be noticed that pertussis-immunized mice, when injected with doses of histamine close to the LD_{100} of normal mice, will also die from these challenge doses.

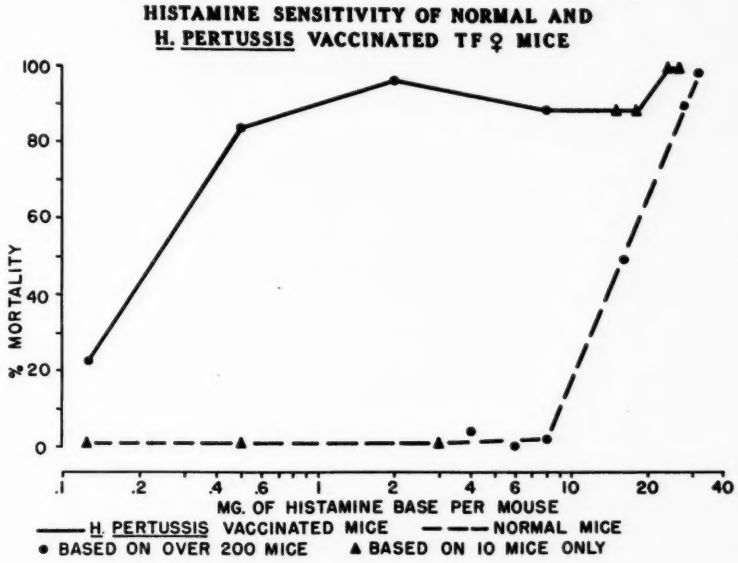

Fig. 1.

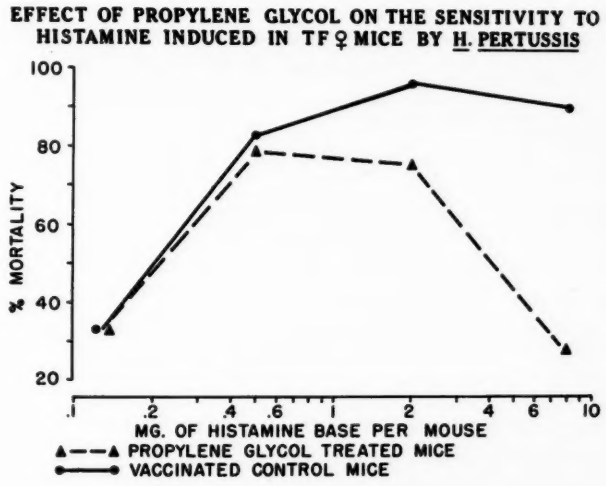

Fig. 2.

When mice vaccinated with *H. pertussis* are treated during the sensitization period with 0.1 ml. of 80 per cent water solution of propylene glycol, four consecutive days starting on the day of immunization, it is found that a large number of mice survive the high challenge doses of histamine while most mice injected with lower doses die. The accumulated results of two such experi-

ments are given in Fig. 2 where each point represents 20 mice. It can readily be seen that propylene glycol treated mice were resistant to 8 mg. of histamine (26 per cent mortality) while highly sensitive to 0.5 mg. of histamine (80 per cent mortality). It was important to determine whether this phenomenon was specific for propylene glycol or if it was a response of the pertussis-vaccinated mice to the injection of other substances as well. The following experiment was performed to answer this question.

TF female mice were immunized with 2 billion *H. pertussis* cells and groups of 40 mice were treated for four consecutive days starting on the day of immunization with one of the following substances: 5 per cent soluble starch solution, 0.5 per cent acetylsalicylic acid (aspirin), 0.005 per cent colchicine, physiologic saline solution adjusted to pH 11.3 with 0.1N NaOH, 1 per cent solution of carboxymethyl cellulose (CMC), and 0.5 per cent glucose. All of these solutions were made in physiologic saline solution. Twenty-four hours after the last treatment with these substances the various groups of mice were challenged with graded doses of histamine. The amounts of each substance injected and the results obtained at the 0.5 and 8 mg. challenge doses of histamine are given in Table I. As can be seen from this table, 5 per cent starch, 0.5 per cent aspirin, 1 per cent CMC, 0.005 per cent colchicine, and alkaline saline solution at pH 11.3 produced the phenomenon to a greater or lesser extent. From the unrelated nature of these substances it is apparent

TABLE I. EFFECT OF VARIOUS SUBSTANCES ON THE SENSITIVITY TO HISTAMINE INDUCED BY H. PERTUSSIS*

SUBSTANCE†	CONCENTRATION USED (%)	VOLUME INJECTED PER MOUSE (ML.)	HISTAMINE BASE CHALLENGE PER MOUSE			
			0.5 MG. D/T		8.0 MG. D/T	
			TREATED	CONTROL	TREATED	CONTROL
Starch	5	0.5	5/10	6/10	2/9	9/10
Colchicine	0.005	0.2	10/10	9/10	5/10	9/10
Carboxymethyl cellulose	1	0.2	7/10	6/10	1/10	9/10
Alkaline saline pH 11.3 adjusted with 0.1 N NaOH	–	0.2	7/9	7/10	2/10	6/10
Acetylsalicylic acid	0.5	0.2	10/10	–	2/10	–
Glucose	5	0.2	10/10	–	9/10	–

D/T, Deaths over total injected.

*Each mouse received intraperitoneally the amount of substance indicated on four consecutive days. The challenge with histamine was carried out twenty-four hours after the last treatment.

†All solutions were made in physiologic saline solution.

that this phenomenon is nonspecific and can be produced by the injection of a variety of materials. Glucose, 0.5 per cent, in the amount used did not produce the high survival at the 8 mg. dose of histamine. It was important to determine whether a different type of stress could also produce this phenomenon. To this end mice injected with *H. pertussis* were "sham" adrenalectomized under ether anesthesia and then tested for their histamine sensitivity twenty-four hours after the operation. The results are given in Table II where

TABLE II. EFFECT OF SHAM OPERATION UNDER ETHER ANESTHESIA ON THE HISTAMINE SENSITIVITY OF MICE VACCINATED WITH H. PERTUSSIS

HISTAMINE	*H. pertussis* SENSITIZED D/T		*H. pertussis* SENSITIZED + SHAM OPERATED 24 HOURS BEFORE CHALLENGE	
	1ST EXP.	2ND EXP.	1ST EXP.	2ND EXP.
0.125	0/10		1/10	
0.5	8/10	15/20	5/10	10/20
2	9/10		7/9	
8	9/10	15/20	6/10	6/19

it can be seen that the "sham" operated animals were more resistant to high doses of histamine than to lower doses.

It was of interest to find whether the mice surviving the high doses of histamine were sensitive to smaller doses of the same drug. Therefore, mice that, from previous experiments, had survived the 8 mg. dose of histamine were rechallenged five days later with various doses of histamine as given in Table III. It can readily be seen that these mice were resistant to 8 mg. of histamine but sensitive to lower doses of the drug.

TABLE III. HISTAMINE SENSITIVITY OF PERTUSSIS-SENSITIZED MICE SURVIVING THE 8 MG. CHALLENGE DOSE OF HISTAMINE

MG. HISTAMINE PER MOUSE	D/T
0.5	5/10
2	7/9
8	2/9

DISCUSSION

The results presented in this article indicate clearly that *H. pertussis*-injected mice develop a sensitivity to histamine which is peculiar in that more mice injected with lower doses (0.5 to 2 mg./mouse) die than those injected with higher doses (4 to 8 mg.) of the same drug. This phenomenon is not marked and in individual experiments it may not be at all apparent when death of the animals is taken as the end point. But even in experiments with high mortality it has been observed that mice injected with 4 to 8 mg. of histamine survive for longer periods of time than those injected with 0.5 to 2 mg. This phenomenon can be markedly increased to obtain actual survivals if the immunized mice are treated with a variety of substances including 5 per cent starch and dilute NaOH. Injections of 0.5 per cent glucose or 1 per cent starch have not shown this effect. The substances thus far studied which give this phenomenon are quite diverse, and have little in common. Since sham adrenalectomy (and perhaps even ether anesthesia alone) may produce this unusual dose-response curve, it is suggested that these substances exert their effect through the production of similar nonspecific stress reactions. Although none of these compounds was injected in quantities even approaching its lethal toxic dose, it is conceivable that the amounts given were sufficiently toxic to serve as stress-producing agents.

It is at present difficult to explain why more mice should survive when given higher doses of histamine than those producing nearly 100 per cent

death of the animals. It is tempting, however, to postulate that histamine at a critical concentration (in our experiments this must be 8 mg. or close to this amount given intraperitoneally) stimulates a mechanism that is capable of either destroying histamine or making the mice more resistant to this drug. What this mechanism may be is not known, but it does not involve the adrenal glands since it has been shown[12] that adrenalectomized mice which become highly sensitive to histamine also give this peculiar response.

SUMMARY

1. Mice immunized with *H. pertussis* are slightly more resistant to high doses of histamine (8 mg.) than they are to lower doses (0.5 to 2 mg.).

2. The resistance of these mice to high doses of histamine can be greatly increased by treating the mice with propylene glycol, 5 per cent starch, 0.005 per cent colchicine, 0.5 per cent aspirin, and weak NaOH solutions, etc.

3. Normal mice do not give this type of response to histamine.

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SENSITIVITY TO HISTAMINE OF ADRENALECTOMIZED MICE FROM DIFFERENT STRAINS

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NORMAL mice are highly resistant to the injection of histamine in contrast to the guinea pig, that is very sensitive to this substance.[1-3] Adrenalectomy has been shown to increase markedly the sensitivity of mice to histamine,[4, 5] and this sensitivity can be prevented by the injection of cortisone and epinephrine.[4, 5]

In the present report we have confirmed the observation that adrenalectomized mice can become highly sensitive to the injection of small amounts of histamine, but it was found that not all strains of mice become sensitive to this drug after the removal of the adrenal glands. In addition it has been observed that the average adrenalectomized mouse of the "sensitive strains" is more susceptible to small doses of histamine than to larger doses of the same drug. The experiments on which these conclusions are based are reported here.

MATERIALS AND METHODS

Mice.—Three different strains of mice have been used. The Swiss-Webster strain purchased from the Tumblebrook Farms, New York (TF); the NIH strain of mice purchased from the Beverly Farms, New Jersey (BF); and the CF-1 strain purchased from the Carworth Farms, New York (CF). All the mice used were females weighing 16 to 20 grams.

Adrenalectomy.—The mice were adrenalectomized bilaterally under ether anesthesia by making one large incision through the skin along the spine and then two small incisions through the peritoneal wall at the level just below the ribs and above each kidney. The adrenal glands were carefully and completely removed with two pairs of fine blunt-end forceps. The skin incision was sutured with fine cotton thread. No attempt was made to suture the two small peritoneal incisions. The mortality due to this operation was less than 10 per cent. Only mice completely recovered from the operation were used in the experiments. The mice were given saline solution instead of water to drink. Adrenalectomized mice have been kept under these conditions for a number of days without any signs of illness. To control the effects of the operation on histamine sensitivity, mice have also been "sham" adrenalectomized. These mice were subjected to the above procedure except for the removal of the adrenal glands.

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Histamine Challenge.—The challenge with histamine was given intraperitoneally in a total volume of 0.5 ml. of saline. Graded doses of histamine base (given as histamine diphosphate)* were used and ten mice, usually, were injected with each dose of the drug. Normal mice were also challenged intraperitoneally with graded doses of histamine to serve as controls. The pH of the histamine solutions used ranged from 4.5 in solutions containing 1 mg. histamine base per milliliter to 4.0 in solutions containing 24 mg. per milliliter.

RESULTS

In the first experiment, the sensitivity of adrenalectomized mice of three different strains (CF, TF, and BF) was studied. The mice were bilaterally adrenalectomized and 24 hours later challenged with graded doses of histamine as shown in Table I. From this table it can be seen that the TF and the BF

TABLE I. HISTAMINE SENSITIVITY OF ADRENALECTOMIZED MICE OF VARIOUS STRAINS

MG. HISTAMINE BASE/MOUSE	STRAIN OF MICE*		
	TF	BF	CF
0.031	0/10†		0/10
0.125	3/10	2/10	0/10
0.5	10/10	7/10	0/10
2.0	7/10	8/10	0/10
4.0	—	2/10	0/10
8.0	3/10	5/10	2/10

*The LD_{50} of normal mice was found to be 16.24 mg. for the TF strain, 13.8 mg. for the BF strain, and 15.5 mg. of histamine base for the CF strain.
†Deaths/Total injected.

mice became highly sensitive to histamine when adrenalectomized. The CF mice, however, did not become sensitive to histamine after adrenalectomy. It is interesting to note that there is no relationship between the LD_{50} of histamine for normal mice and their ability to become sensitive to histamine after adrenalectomy. Sham adrenalectomized mice of the most sensitive strain (TF) do not become sensitive to histamine as shown in Table II.

The resistance of adrenalectomized mice of the CF strain to histamine is apparently not due to unmetabolized substances produced by the adrenal glands, that may be present in excess in the tissues of CF mice, since these mice were equally resistant to histamine when challenged four days after

TABLE II. EFFECT OF SHAM ADRENALECTOMY ON HISTAMINE SENSITIVITY OF TF FEMALE MICE

HISTAMINE BASE MG./MOUSE	DEATHS/TOTAL*
0.5	0/10
2.0	0/10
4.0	0/10
8.0	0/10
12.0	4/10
18.0	10/10
27.0	10/10
40.5	10/10

*The LD_{50} for sham adrenalectomized mice calculated from this experiment is 12.8 mg., while the LD_{50} for normal TF female mice has been found to be 13.8 mg. of histamine base. This difference is not significant.

*Purchased from the Reade Manufacturing Co., Jersey City, N. J.

adrenalectomy. It is possible, however, that this strain of mice may have accessory adrenal tissue as that observed by others in rats[5] as well as mice[6] which could be responsible for their resistance.

During the experiments performed over a period of time with both the TF and the BF mice, it was observed that when the adrenalectomized mice were challenged with graded doses of histamine more mice died at the lower challenge doses (0.5 to 2 mg. per mouse) than at the higher challenge doses (8 mg. histamine base per mouse). The results of sixteen experiments in which graded doses of histamine were given intraperitoneally to adrenalectomized mice of the TF strain are given in Table III. From this table it can be seen that of the sixteen experiments, thirteen gave fewer deaths at the 8 mg. dose than at the 2 or 0.5 mg. of histamine. The negative linear trend of these results was found to be statistically significant ($P < 0.01$).

TABLE III. RESPONSE OF ADRENALECTOMIZED TF FEMALE MICE TO GRADED DOSES OF HISTAMINE GIVEN INTRAPERITONEALLY

EXP. NO.	DOSE OF HISTAMINE BASE* PER MOUSE		
	0.5 MG.	2.0 MG.	8.0 MG.
1	8/10†	7/9	5/10
2	10/10	8/10	8/10
3	10/10	10/10	8/10
4	6/10	8/10	6/10
5	9/10	8/10	6/10
6	8/10	9/10	9/10
7	9/10	10/10	8/10
8	7/10	9/10	9/10
9	10/10	7/10	3/10
10	8/10	8/9	9/10
11	8/9	9/9	4/9
12	7/10	8/10	5/10
13	7/10	4/10	3/10
14	5/10	6/10	4/10
15	6/7	8/10	5/10
16	7/10	7/10	4/10
Combined % Death	80.0	80.0	60.0

*Given as histamine diphosphate.
†Deaths/Total mice challenged.

Normal mice injected with graded doses of histamine do not give this type of response, even when the histamine dose is increased to 48 or 96 mg. of histamine base per mouse as shown in Table IV.

TABLE IV. EFFECT OF LARGE DOSES OF HISTAMINE ON NORMAL TF MICE

HISTAMINE BASE MG./MOUSE	D/T
12	2/10
24	8/10
48	10/10
96	10/10

Since all the injections of histamine were given intraperitoneally in the previous experiments, it was of interest to know whether the same type of response was obtained by the intravenous route. Therefore, adrenalectomized TF female mice were challenged intravenously 24 hours after the operation

with graded doses of histamine in a volume of 0.2 ml. and the deaths recorded 24 hours after the challenge. Table V gives the results obtained in 3 different experiments. It is evident from these data that histamine given intravenously also produces the same phenomenon, although as expected, less histamine is required by this route than by the intraperitoneal route. The responses for doses 0.405 mg. and 1.215 mg. of experiments 1 and 2 and those for doses 0.24 mg. and 0.96 mg. of experiment 3 were analyzed statistically. The analysis indicates a significant negative slope ($P < 0.05$) for the two doses selected from each experiment.

TABLE V. RESPONSE OF ADRENALECTOMIZED TF FEMALE MICE TO GRADED DOSES OF HISTAMINE GIVEN INTRAVENOUSLY

EXPERIMENT 1		EXPERIMENT 2		EXPERIMENT 3	
DOSE* MG./MOUSE	D/T†	DOSE MG./MOUSE	D/T	DOSE MG./MOUSE	D/T
0.005	0/10				
0.015	0/10			0.015	4/10
0.045	4/10	0.045	3/10	0.06	6/10
0.135	4/10	0.135	5/10	0.24	9/10
0.405	8/10	0.405	7/10	0.96	4/10
1.215	3/10	1.215	4/10	3.84	9/10
3.645	10/10				

*Histamine base given as histamine diphosphate.
†Deaths/Total mice challenged.

DISCUSSION

From the results presented in this paper, it is clear that although some strains of mice become highly sensitive to histamine after their adrenal glands are removed, other strains do not. This observation points out the importance of the strain of mice in experiments of this nature.

It is difficult to explain the difference in response to histamine that adrenalectomized mice of different strains give, and at present the only explanation that can be offered is that the CF strain of mice may have highly developed accessory adrenal tissue which takes over the function of the adrenal glands immediately after adrenalectomy. Accessory adrenal tissue has been observed in normal mice of various strains by Spiers.[6] We have observed it grossly and histologically 20 days after adrenalectomy in the CF and the TF strains of mice,[8] and at present we are investigating the possibility of demonstrating qualitative or quantitative differences in normal mice of these two strains with respect to the presence of accessory adrenal tissue.

The paradoxical survival of adrenalectomized mice, when injected with histamine doses higher than those that produce nearly 100 per cent deaths of the animals, is unexplained. It seems possible from the results presented that the adrenal glands are not the only organs concerned in the protection of mice to histamine. There may be another mechanism, perhaps stimulated by a critical concentration of histamine, that comes into play when this concentration of the drug has been reached. It is of interest to find that *Hemophilus pertussis* sensitized mice of the TF and BF strain of mice which become highly sensitive to histamine[9] also show this phenomenon.[10]

SUMMARY

1. After adrenalectomy, mice of the TF and BF strains become highly sensitive to histamine, but mice of the CF strain do not respond in this manner.

2. A paradoxical response to histamine was demonstrated in mice made sensitive to this drug by adrenalectomy. It was shown that a greater percentage of mice survived higher doses of histamine than those producing nearly 100 per cent deaths of the animals. No such response was obtained with normal mice.

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PREPONDERANT ROLE OF ANTIPLATELET ANTIBODY IN THE INDUCTION OF SHOCK BY ANTIPLATELET SERUM*

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SINCE Forssman antibody has been detected in antiplatelet serum (APS)[1, 2] and since this antibody is able to produce a shocklike condition in the guinea pig,[3] it was thought worth while to find out to what extent this antibody is responsible for the shock induced by APS,[4, 5] especially if it is taken into consideration that the behavior of platelets and other hematological data, as well as blood pressure determinations,[6] absence of histamine in the blood stream,[7] blood volume studies[8] and detailed observations of the pathologic anatomy[9] in the APS shock already have been published without taking into account the presence of the Forssman antibody in the APS used in these studies.

METHODS

Antiplatelet serum was obtained by injecting rabbits intravenously with washed dog platelets according to the technique described by Tocantins.[10] Forssman antibody was produced in rabbits after intravenous injection of the supernatant of a saline guinea pig kidney extract.[11] The quantitative determination of the APS potency was performed in vitro by a technique developed at this laboratory, applying the property of APS to lyse platelets in the presence of complement by timing the decrease of turbidity of a platelet suspension in the presence of APS and complement in a photoelectric apparatus.[12] Quantitative determinations of Forssman serum were obtained by observing the amount of sera necessary to hemolyze 50 per cent of 0.1 ml. of a 2 per cent sheep red blood cell suspension in the presence of 0.1 ml. of a 1/10 dilution of guinea pig serum made up to 1 ml. with saline, after 15 minutes' incubation at 37° C.[2] One hundred times the amount of serum necessary to induce 50 per cent hemolysis under the test conditions was arbitrarily chosen as a Forssman unit.

Platelet determination was performed by a method which separates the platelets from other blood elements by fractional centrifugation and measuring the light absorption of a volume of the platelet suspension in a photoelectric spectrophotometer.[13] Light absorption was correlated to platelet volume obtained by the Van Allen thrombocytocrit[14] and results were presented as platelet volume in 100 ml. of blood.

Arterial pressure was registered on a Ludwig manometer connected to the carotid artery using a 5 per cent sodium citrate solution as an anticoag-

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ulant. Hemoglobin was determined colorimetrically in a Unicam spectrophotometer (Cambridge) as oxyhemoglobin. Wintrobe tubes were used for the hematocrit determinations, readings being made after centrifuging for one-half hour at 3,000 rpm. With regard to blood gases, determinations of O^2 and CO^2 concentration for both arterial and venous blood were made with the manometric apparatus of Van Slyke.[15] Lactic acid was determined by the method described by Barker and Summerson.[16]

RESULTS

Amount of Forssman Serum Required to Induce Shock in the Dog.—A typical case is shown in the experiment presented in Table I.

TABLE I. HEMATOLOGICAL, BIOCHEMICAL, AND BLOOD GAS DETERMINATIONS IN SHOCK INDUCED BY STANDARD FORSSMAN ANTIBODY (154 FORSSMAN UNITS PER KILOGRAM)*

MINUTES AFTER ONSET OF SHOCK	ARTERIAL PRESSURE MM. HG	CO^2 (VOL. %)		O^2 (VOL. %)		HB (GR. %)		VENOUS HB SATURATION (%)	ARTERIAL HEMATOCRIT (%)	LACTIC ACID (MG./100 ML.)
		ARTERIAL	VENOUS	ARTERIAL	VENOUS	ARTERIAL	VENOUS			
0	142	37.7	36.1	18.4	14.0	11.0	10.8	-	38	16.0
3	40	-	-	-	-	-	-	-	-	-
10	122	29.8	32.3	17.2	15.4	10.8	11.0	-	39	20.0
60	116	26.5	31.3	18.1	9.4	11.4	11.8	59	43	23.0
100	26	13.5	25.2	19.3	8.2	11.8	11.8	52	44	34.5
150	76	11.4	22.8	20.3	6.0	12.0	12.4	36	45	38.0
240	70	9.3	19.4	19.8	5.0	11.7	-	-	43	48.0

*Dog 795. Weight: 9.7 kg. Platelets: 0.82 ml./100 ml. blood. Anesthesia by Thionembutal (1.4 ml./kg. of body weight, in a 1.5 per cent saline solution).

In keeping with a previous study,[6] the classification of shock induced by the amount of Forssman antibody used (154 Forssman units per kilogram) should be called mild.

Changes Induced by the Average Amount of Forssman Antibody Present in Potent Samples of Antiplatelet Serum.—Eleven samples of potent antiplatelet serum (average of 300 units per milliliter) had an average of 7.1 Forssman units per milliliter. When 200 antiplatelet serum units per kilogram of body weight are taken as a dose producing a severe shock, the amount of Forssman

TABLE II. 0.9 ML. OF STANDARD FORSSMAN SERUM WITH A TITER OF 40 FORSSMAN UNITS PER MILLILITER (4.8 FORSSMAN UNITS PER KILOGRAM) INJECTED IN THE SAPHENOUS VEIN*

MINUTES AFTER ONSET OF SHOCK	ARTERIAL PRESSURE MM. HG	CO^2 (VOL. %)		O^2 (VOL. %)		HB (GR. %)		VENOUS HB SATURATION (%)	ARTERIAL HEMATOCRIT (%)	LACTIC ACID (MG./100 ML.)
		ARTERIAL	VENOUS	ARTERIAL	VENOUS	ARTERIAL	VENOUS			
0	147	35.4	36.9	18.5	13.6	14.5	13.5	76	47	19.7
3	110	-	-	-	-	-	15.0	-	-	-
60	140	26.9	34.3	21.4	11.0	15.7	15.0	55	49	39.3
120	140	26.6	33.6	21.1	10.0	14.5	15.0	50	47	74.8
180	150	28.4	35.9	20.7	11.7	15.0	14.5	60	43	-
240	150	28.7	34.9	20.7	12.4	14.0	14.5	64	-	-

*Dog 820. Weight: 7.3 kg. Platelets: 0.56 ml./100 ml. blood. Anesthesia by Thionembutal (3.5 ml./kg. of body weight, in a 1.5 per cent saline solution).

units contained in this amount of antiplatelet serum corresponds to 4.8 Forssman units per kilogram. The experiment in Table II employed standard Forssman antibody in an amount corresponding to 4.8 Forssman units per kilogram.

The results in Table II show that the amount of standard Forssman antibody tested was insufficient to cause shock.

Effect of the Absorption of the Forssman Antibody From Potent APS Samples.—In Table III is presented a typical example taken from several cases in which the Forssman antibody was completely absorbed from APS by sheep red blood cells.

TABLE III. APS ABSORBED WITH SHEEP RED BLOOD CELLS (200 LYTIC UNITS PER KILOGRAM OF BODY WEIGHT). DEATH EIGHT HOURS AFTER APS INJECTION*

MINUTES AFTER ONSET OF SHOCK	ARTERIAL PRESSURE MM. HG	CO_2 (VOL. %)		O_2 (VOL. %)		HB (GR. %)		VENOUS HB SATURATION (%)	ARTERIAL HEMATOCRIT (%)	LACTIC ACID (MG./100 ML.)
		ARTERIAL	VENOUS	ARTERIAL	VENOUS	ARTERIAL	VENOUS			
0	128	-	36.3	-	12.1	-	12.5	73	41	4.5
3	26	-	-	-	-	-	-	-	-	-
7	40	-	31.1	-	6.8	-	9.1	56	-	-
20	66	-	30.9	-	1.3	-	10.5	9	35	29.5
60	76	-	27.8	-	2.3	-	12.1	14	40	49.0
120	-	-	23.9	-	8.7	-	12.5	51	41	42.5

*Dog 729. Weight: 9.0 kg. Platelets: 0.33 ml./100 ml. blood. Anesthesia by Thionembutal (2.0 ml./kg. of body weight, in 1.5 per cent saline solution).

According to the previous classification, this shock should be called severe.

Effect of Absorption of Forssman Antibody and Antidog Hemolysin From Potent APS Samples.—As was to be expected, even with careful separation of platelets to be injected into rabbits to obtain APS, a few dog red blood cells always are injected with the platelets; this seems to explain why APS has also some slight hemolytic action toward the red cells of dogs. To study the possible role of this hemolysin in the production of shock by APS, we have absorbed samples with dog red blood cells, in addition to the previous absorption with sheep red cells, to remove the Forssman antibody. Several dogs were subjected to shock by the same procedure, since we used to absorb our APS samples routinely with dog and sheep erythrocytes. An example of shock by the doubly absorbed APS is presented in Table IV.

TABLE IV. APS ABSORBED WITH DOG AND WITH SHEEP ERYTHROCYTES (150 LYTIC UNITS PER KILOGRAM). DEATH EIGHTY-FIVE MINUTES AFTER THE APS INJECTION*

MINUTES AFTER ONSET OF SHOCK	ARTERIAL PRESSURE MM. HG	CO_2 (VOL. %)		O_2 (VOL. %)		HB (GR. %)		VENOUS HB SATURATION (%)	ARTERIAL HEMATOCRIT (%)	LACTIC ACID (MG./100 ML.)
		ARTERIAL	VENOUS	ARTERIAL	VENOUS	ARTERIAL	VENOUS			
0	140	36.2	38.2	16.6	12.3	-	13.2	70	46	-
2	25	-	-	-	-	-	-	-	-	-
60	65	9.8	22.6	19.0	4.2	-	14.4	22	49	138.4

*Dog 827. Weight: 7.1 kg. Platelets: 0.36 ml./100 ml. blood. Anesthesia by Thionembutal (1.7 ml./kg. of body weight, in a 1.5 per cent saline solution).

This should be interpreted as severe shock, not only on account of the gas and lactic acid determinations, but also because of the short time of survival.

DISCUSSION

The results show that the amount of Forssman antibody which is injected with the antiplatelet antibody is not sufficient to produce any of the signs found in this type of shock. However, in appropriate amounts the Forssman antibody can produce symptoms of shock in dogs, as Forssman[3] has shown for the guinea pig. The property of inducing two different shock substances is probably common to platelets of the animals showing the Forssman antigen as a constituent of these blood elements.[2] That the most potent of these shock substances is not the Forssman antibody could be inferred by the shock produced in rabbits and rats,[4, 5] animals in whose platelets the Forssman antigen could not be detected.[1, 2]

The small amount of hemolysin built up during the immunizing process, probably by contamination of the injected platelets with dog red blood cells, seems not to be responsible for any of the characteristic findings of this shock. Even the hemolysis found in vivo toward the end of the shock period is not due to this hemolysin, since it is also found when the antiplatelet serum is injected after previous absorption with dog erythrocytes.

The absence of a significant effect of the Forssman and of the hemolytic antibodies is shown more clearly by the action of the antiplatelet serum previously absorbed by sheep and dog red cells. The amount of APS, after absorption with these erythrocytes, needed to induce shock is the same as it was before the absorption. Nevertheless, for detailed studies of antiplatelet serum shock it is advisable to absorb the APS to avoid any unknown interference of these secondary antibodies.

SUMMARY

The amounts of other antibodies different from the antiplatelet antibody found in APS were of no practical significance in the production of shock by APS. The severity of shock and its general characteristics are directly proportional to the amount of the antiplatelet antibody injected intravenously, no account being taken of small variations of individual sensitivity in the dogs subjected to the experiment.

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THE CLINICAL TOXICITY OF ANTIBIOTICS AND SULFONAMIDES

A Comparative Review of the Literature Based on 104,672 Cases Treated Systemically*

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A PREVIOUS article[1] reviewed statistically the literature from 1936 to Nov. 1, 1950, concerning the manifestations of toxicity observed during and after the systemic administration of the following antibacterial agents: Aureomycin, Chloromycetin, dihydrostreptomycin, penicillin, streptomycin, sulfadiazine, sulfaguanidine, sulfamerazine, sulfanilamide, sulfapyridine, Sulfasuxidine, sulfathiazole, and Terramycin. At the same time the literature on Chloromycetin and Terramycin from Nov. 1, 1950, to April 15, 1951, was also reviewed. In accompanying studies the literature of the same period on the oral manifestations of toxicity following antibacterial therapy[2] and the unusual toxic reactions reported in individual case reports[3] were similarly reviewed in detail.

The present cumulative article (which includes all of the data summarized and tabulated in the initial report[1]) reviews, in addition, the literature on the clinical manifestations of toxicity following the systemic administration of Aureomycin, Chloromycetin, and Terramycin as reported in the literature from April 15, 1951, to Jan. 1, 1953; also included is a review of the literature on Elkosin, gantrisin, Magnamycin, Ilotycin, neomycin, bacitracin, and polymixin B from the time of the appearance of published reports on these drugs until Jan. 1, 1953. The literature up to October, 1953, on Magnamycin and Ilotycin, and on gantrisin up to May, 1953, has been included also. Only articles written in the English language were reviewed except in the literature on Elkosin.

Tables I and II summarize nearly all of the large clinical studies involving Aureomycin, Chloromycetin, penicillin, streptomycin, sulfadiazine, sulfaguanidine, sulfamerazine, sulfanilamide, sulfapyridine, sulfasuxidine, sulfathiazole, and Terramycin, as well as nearly every published clinical report which included more than five cases on the systemic administration of bacitracin, Elkosin,

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TABLE

TOTAL NUMBER CASES SYMPTOMS*	AUREOMYCIN 3,121			BACITRACIN (188)			CHLOROMYCETIN 2,968			ELKOSIN 994		
	A	B	C	A	B	C	A	B	C	A	B	C
1. *General*												
2. Acidosis	85	1.18	0.03									
3. Cephalgia	8	12.50	0.03	21	14.29	1.60	105	4.76	0.17			
4. Aggravation of symptoms							69	34.78	0.81			
5. Cyanosis	39	12.82	0.16									
6. Fever and chills										848	0.24	0.20
7. Flushing and heat (hyperemia)												
8. Burning							30	6.67	0.07			
9. Jaundice (*hepatic and hemolytic)							15	0	0			
10. Edema	200	1.00	0.09				30	3.33	0.03			
11. Malaise (*faintness, fullness, lassitude, weakness)							100	3.00	0.10			
12. Pruritus	92	5.43	0.16									
13. Sweating							13	53.85	0.24			
14. Testicular complaints (tingling pain, epididymitis)												
15. Backache												
16. *Allergic Manifestations*												
17. Sensitivity reactions												
18. Asthma												
19. Herxheimer reaction	271	2.95	0.26				17	29.41	0.17			
20. Id reaction												
21. Serum sickness-like (anaphylactoid reaction)							59	1.68	0.03			
22. Skin sensitivity				24	16.27	2.13	22	0	0			
23. Urticaria	223	2.24	0.16				66	9.09	0.20	350	0.29	0.10
24. Arthralgia and arthritis												
25. *Cardiac Complications*												
26. Bradycardia												
27. Circulatory disorder (*collapse, drop blood pressure)	24	8.33	0.06				33	12.12	0.13			
28. Precordial pain												
29. Tachycardia, palpitation												
30. Hypertension												
31. *Eye Signs*												
32. Conjunctivitis							33	12.12	0.13			
33. Miscellaneous (*episcleritis, iritis, injected sclera)												
34. Visual disturbances (*vision loss, filmy vision, yellow vision)							87	4.60	0.13			
35. *Gastrointestinal Disturbances*				24	8.33	1.06	59	1.68	0.03	496	4.44	2.21
36. Abdominal distention	393	2.80	0.35	100	1.00	0.53	116	27.59	1.08			
37. Abdominal pain	94	5.32	0.16	24	16.67	2.13	457	6.78	1.04			
38. Anorexia and indigestion	150	8.67	0.42	24	4.17	0.53	420	8.33	1.18			
39. Vomiting and/or nausea	2,344	23.34	17.53	24	4.17	0.53	1,495	5.62	2.83	498	0.80	0.40
40. Diarrhea	1,571	9.61	4.84	100	2.00	1.06	962	5.09	1.63			
41. Gastritis							41	2.44	0.03			
42. Gastroenteritis							25	8.00	0.07			
43. Miscellaneous												
44. Intestinal hemorrhage (*bloody diarrhea)												
45. Hemorrhoids	135	4.44	0.19									
46. Proctitis (*pruritus ani anal fissure, perianal fissure, anal irritation)	635	3.62	0.74	24	8.33	1.06	284	3.17	0.03			
47. *Hematologic Changes*										350	0	0
48. Anemia							231	1.29	0.10			
49. Acute hemolytic anemia												
50. Blood dyscrasias (other)	393	0	0				449	0.45	0.06			
51. Eosinophils	135	0.74	0.03				70	2.86	0.13			

I

ERYTHROMYCIN 74			GANTRISIN 2,010			MAGNAMYCIN 148			NEOMYCIN 405			PENICILLIN 18,519			POLYMYCIN B 75		
A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
									30	23.33	1.73	12,600	0.63	0.43			
			489	2.04	0.50							1,724	10.38	0.97			
			1,239	0.73	0.45				30	33.33	2.47	15,775	6.25	5.32	48	62.50	40.00
			25	4.00	0.05							10,420	0.62	0.35			
												182	0.55	0.01			
			31	6.45	0.10							124	3.23	0.02			
			237	2.11	0.25	15	6.67	0.67				10,420	0.62	0.35	6	33.33	2.67
												10,420	0.13	0.07	6	100.00	8.00
												182	0.55	0.01			
												10,920	0.05	0.03			
			112	1.79	0.10							182	0.55	0.01	32	78.13	33.33
												10,420	0.02	0.01			
												7,906	55.45	-			
												900	0.89	0.04			
												11,044	0.10	0.06			
			1,143	0.17	0.10	57	5.26	2.02				13,338	1.40	1.00	6	100.00	8.00
												10,420	0.16	0.09			
			25	4.00	0.05										6	16.67	1.33
			106	0.94	0.05												
									30	10.00	0.74				6	16.67	1.33
33	3.03	1.35															
						58	5.17	2.02									
			1,122	0.80	0.45	30	16.67	3.38	30	10.00	0.74						
41	2.44	1.35	1,786	2.02	1.79	124	13.71	11.49	66	7.58	1.23	12,100	0.58	0.38	6	16.67	1.33
						124	13.71	11.49									
												1,724	0.58	0.05			
												10,420	0.17	0.10			
			25	12.00	0.15	15	20.00	2.02									
56	0	0							26	0	0						
			175	1.14	0.10												
7	0	0	93	3.23	0.15				26	0	0						

TABLE I—CONT

TOTAL NUMBER CASES SYMPTOMS*	AUREOMYCIN 3,121			BACITRACIN (188)			CHLOROMYCETIN 2,968			ELKOSIN 994		
	A	B	C	A	B	C	A	B	C	A	B	C
52. Leukocytosis	13	7.69	0.03							350	0	0
53. Leukemoid												
54. Leukopenia	135	0.74	0.03									
55. Granulocytopenia (*neutropenia, agranulocytosis)							214	0	0			
56. Thrombocytopenia (*thrombocytopenic purpura)												
57. Thrombosis of vein												
58. *Hepatic Damage-Hepatitis* (*hepatitis, ascites)	304	0.33	0.03									
59. *Local Reactions* (*thrombophlebitis, soreness, necrosis, slough, transient pain)							28	21.43	0.20			
60. Myalgia												
61. *Neurological Disturbances*												
62. Mental disorders and psychoses (*confusion, disorientation, drunkenness, C.N.S. dist.)							96	4.17	0.13			
63. Cerebral stimulation (*mental irritation, tenseness, nervousness, insomnia)	36	11.11	0.13									
64. Depression (*drowsiness)	308	3.57	0.35							350	0	0
65. Neurological disorders	209	0	0									
66. *Auditory Disturbances* (tinnitus, deafness—temporary and permanent, partial and total)												
67. Encephalopathy (*toxic neuropathy)												
68. Peripheral neuritis (*nerve palsy, nerve root pain)												
69. Paresthesia (*numbness—fingers, legs, toes, hyperesthesia)	108	0.93	0.03									
70. Vertigo	401	2.74	0.35				399	4.76	0.64			
71. Vestibular disturbances (*eighth nerve damage ataxia)								**				
72. *Oral Disturbances*	99	7.07	0.22				129	29.46	1.28			
73. Stomatitis	134	22.90	0.90				987	4.15	1.38			
74. Glossitis	298	1.34	0.13				413	11.86	1.65			
75. Cheilosis	262	2.29	0.19				293	3.41	0.34			
76. Tongue discoloration	319	2.19	0.22				200	2.00	0.13			
77. Metallic taste	16	12.50	0.06									
78. Bitter taste							428	15.89	2.29			
79. *Respiratory Disturbances* (*dyspnea, breathlessness, respiratory failure)												
80. Pharyngitis	99	7.07	0.22				121	7.44	0.30			
81. *Skin Reactions*												
82. Dermatitis	222	1.80	0.13				149	6.04	0.30			
83. Desquamative and exfoliative dermatitis	245	1.63	0.13									
84. Dermatitis venenata												
85. Photosensitivity	150	2.67	0.13				46	8.70	0.13			
86. Vulvovaginitis and vaginitis	123	12.20	0.48				201	5.97	0.40			
87. Rash (*scarlatino, fleeting erythema)	670	2.99	0.64				525	3.62	0.64	848	2.00	1.71
88. *Urinary System Disturbances*												
89. Bladder irritation (*burning urination)	245	6.63	0.51				71	8.45	0.20			
90. Kidney disturbances (*renal impairment, nephritis, urinary disturbances, nephrotoxicity)	250	0	0	50	2.00	0.53	121	0	0	848	0.83	0.70

TABLE I—CONT'D

ERYTHROMYCIN 74			GANTRISIN 2,010			MAGNAMYCIN 148			NEOMYCIN 405			PENICILLIN 18,519			POLYMYCIN B 75		
A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
			159	8.81	0.70												
			102	2.94	0.15												
												10,420	0	0			
												12,100	2.77	1.81			
												500	0.40	0.01			
			270	3.33	0.45	57	3.51	1.35				182	0.55	0.01	27	0	0
															6	16.67	1.33
1	0	0							241	13.69	8.15				6	16.67	1.33
												10,420	0.11	0.06			
			25	16.00	0.19				30	33.33	2.47				6	16.67	1.33
			25	4.00	0.05	15	6.67	0.68	24	4.17	0.25	1,686	0.18	0.02			
															12	25.00	4.00
															4	25.00	1.33
												51	5.88	0.02			
												297	2.02	0.03			
						57	1.76	0.68				59	6.78	0.02			
			1,484	0.67	0.50							10,420	0.21	0.12			
												10,520	0.06	0.03			
31	0	0	71	1.41	0.05				8	12.50	0.25	2,711	1.92	0.28			
33	0	0	153	0.65	0.05				97	46.39	11.11	36	0	0	69	5.80	5.33

TABLE

TOTAL NUMBER CASES SYMPTOMS•	AUREOMYCIN 3,121			BACITRACIN (188)			CHLOROMYCETIN 2,968			ELKOSIN 994		
	A	B	C	A	B	C	A	B	C	A	B	C
91. Decreased urinary function (*elevated N.P.N., nitrogen retention, azotemia, oliguria, decreased P.S.P.)	36	0	0				85	15.29	0.44			
92. Albuminuria (*cylindruria, urinary casts)	10	10.00	0.03	50	30.00	7.98	15	0	0			
93. Nephrosis												
94. Renal calculi (*kidney stones, renal colic, renal obstruction, crystalluria)							15	0	0			
95. Anuria												
96. Hematuria												
97. Hematuria—microscopic												
98. Hematuria—gross												
99. Renal pain (*loin pain, backache, costovertebral pain)												
Reference Numbers	1-45 368-386			387-390			46-116 358-362 391-412			413-415		

Key:

A, Number of patients studied for the specific reaction.

B, Percentage of patients studied for the specific reaction, who manifested these reactions.

C, Percentage of the total number of patients receiving the antibacterial agent, who manifested the specific reactions.

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*Titles and authors are omitted to save space. Numbers are indexed by specific drugs at the bottom of Tables I and II.

I—CONT'D

ERYTHROMYCIN 74			GANTRISIN 2,010			MAGNAMYCIN 148			NEOMYCIN 405			PENICILLIN 18,519			POLYMYCIN B 75		
A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
			165	0.61	0.05												
									73	6.85	1.23				10	90.00	12.00
												10,420	0	0			
			1,640	1.59	1.29				18	16.67	0.74						
			31	3.23	0.05												
			1,619	0.68	0.55				49	4.08	0.49						
			1,000	0	0												
416-417			418-433			434-439			440-450			117-138			451-455		

*Including.

†Following treatment of spirochetal diseases only.

•When one investigator reported two or more reactions which were grouped together in this article under one symptom, only the largest figure was included.

••For streptomycin all reports of vertigo were included under vestibular disturbances.

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(Bibliography continued on p. 146.)

TABLE II

TOTAL NUMBER CASES SYMPTOMS*	DIHYDRO-STREPTO-MYCIN 462			STREPTOMYCIN 11,305			TERRAMYCIN 3,033			SULFAMER-AZINE 2,875		
	A	B	C	A	B	C	A	B	C	A	B	C
1. *General*												
2. Acidosis												
3. Cephalgia				7,797	2.81	1.94	230	2.61	0.20	381	1.05	0.14
4. Aggravation of symptoms							12	25.00	0.10			
5. Cyanosis												
6. Fever and chills				2,396	15.07	3.19	190	5.79	11.36	2,988	3.15	3.27
7. Flushing and heat (hyperemia)				3,097	3.91	1.07						
8. Burning							7	14.29	0.03	428	3.74	0.56
9. Jaundice (*hepatic and hemolytic)				930	0.22	0.02						
10. Edema							208	0.48	0.03	151	0.66	0.04
11. Malaise (*faintness, fullness, lassitude, weakness)				3,097	0.19	0.05						
12. Pruritus				3,203	0.38	0.11						
13. Sweating				3,097	0.07	0.02						
14. Testicular complaints (tingling pain, epididymitis)				3,097	0.07	0.02						
15. Backache												
16. *Allergic Manifestations*												
17. Sensitivity reactions				72	61.11	0.39						
18. Asthma												
19. Herxheimer reaction												
20. Id reaction												
21. Serum sickness-like (anaphylactoid reaction)												
22. Skin sensitivity												
23. Urticaria				3,169	0.88	0.25						
24. Arthralgia and arthritis				3,803	1.13	0.38				278	0.36	0.04
25. *Cardiac Complications*												
26. Bradycardia												
27. Circulatory disorder (*collapse, drop blood pressure)				3,803	0.47	0.16						
28. Precordial pain												
29. Tachycardia, palpitation				3,134	0.06	0.02						
30. Hypertension												
31. *Eye Signs*												
32. Conjunctivitis										365	1.64	0.21
33. Miscellaneous (*episcleritis, iritis, injected sclera)												
34. Visual disturbances (*vision loss, filmy vision, yellow vision)				7,190	0.28	0.18						
35. *Gastrointestinal Disturbances*												
36. Abdominal distention												
37. Abdominal pain				3,097	0.03	0.01	124	3.23	0.13			
38. Anorexia and indigestion							937	6.94	2.14	135	0.74	0.04
39. Vomiting and/or nausea	195	0.03	0.01	8,152	3.77	2.72	2,231	14.48	10.65	2,425	2.43	2.05
40. Diarrhea				32	2.70	0.01	2,440	14.51	11.67			
41. Gastritis												
42. Gastroenteritis												
43. Miscellaneous										292	0.34	0.04
44. Intestinal hemorrhage (*bloody diarrhea)												
45. Hemorrhoids												
46. Proctitis (*pruritus ani, anal fissure, perianal fissure, anal irritation)							1,098	3.01	1.09			
47. *Hematologic Changes*							36	0	0			
48. Anemia												
49. Acute hemolytic anemia										1,436	0.28	0.14
50. Blood dyscrasias (other)				5,695	0.58	0.29	177	0	0	103	0	0
51. Eosinophils	20	0.30	0.01	10,264	1.89	1.71						

II

SULFADIAZINE 15,852			SULFAGUANIDINE 3,955			SULFANILAMIDE 14,573			SULFAPYRIDINE 10,484			SULFASUXIDINE 1,230			SULFATHIAZOLE 12,863		
A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
															271	0	0
3,071	0.59	0.11	206	5.83	0.30	7,895	2.32	1.26	588	36.05	2.02	61	1.64	0.08	5,777	0.45	0.20
												28	7.14	0.16			
216	0.46	0.01				3,220	20.90	4.62	1,772	6.55	1.11				261	0.38	0.01
13,738	1.57	1.36	2,131	1.78	0.96	13,811	7.70	7.29	6,748	3.38	2.18	1,002	0.80	0.65	7,388	5.59	3.21
100	11.00	0.07	44	6.82	0.08												
1,360	0.07	0.01				2,079	1.15	0.17	100	10.00	0.01				490	0.82	0.03
55	5.64	1.02															
100	30.00	0.19	191	23.56	1.14	7,695	2.08	1.10	450	12.00	0.52				375	0.80	0.02
902	0.44	0.03							380	0.79	0.03	102	1.96	0.16			
															5,037	0.02	0.01
									70	1.43	0.01						
5,500	0.22	0.08	191	1.57	0.08	1,725	0.12	0.01	236	0.85	0.02				100	10.00	0.01
1,063	0.38	0.03				6,176	0.50	0.21	108	0.93	0.01	511	0.78	0.33	1,522	0.59	0.07
						6,170	0.97	0.41							71	2.82	0.02
100	63.00	0.40															
									377	0.80	0.03						
									380	1.05	0.04				360	0.28	0.01
						1,083	0	0									
2,803	0.46	0.08	50	2.00	0.03				797	0.38	0.03				4,970	1.85	0.72
901	0.22	0.01							102	0.98	0.01						
660	0.15	0.01				6,070	0.10	0.04	508	0	0				642	0.31	0.02
						6,070	1.12	0.47	502	2.99	0.14						
500	2.40	0.08	191	2.62	0.13	7,695	1.34	0.71	480	14.79	0.68	50	2.00	0.08			
1,235	1.50	1.17	1,129	1.33	0.38	8,854	2.01	1.22	7,827	39.50	29.49	683	0.88	0.49	11,383	7.12	6.30
						7,795	0.73	0.39	960	0.73	0.07	210	7.14	1.22	1,408	0.64	0.07
						1,625	3.69	0.41	864	0.69	0.49						
									297	0	0				271	0	0
						6,070	0.02	0.01									
												11	3.64	0.33			
			590	0.34	0.05	4,500	1.56	0.48	1,636	2.57	0.04	28	7.14	0.16	993	2.82	0.22
4,207	0.31	0.08				9,202	0.67	0.43	5,376	1.75	0.90				3,265	0.34	0.09
221	0	0	22	0	0	100	0	0				290	0	0	400	0	0
												50	2.00	0.08			

TABLE II—CONTINUED

TOTAL NUMBER CASES / SYMPTOMS •	DIHYDROSTREPTOMYCIN 462			STREPTOMYCIN 11,305			TERRAMYCIN 3,033			SULFAMERAZINE 2,875		
	A	B	C	A	B	C	A	B	C	A	B	C
52. Leukocytosis										428	0	0
53. Leukemoid												
54. Leukopenia	42	0	0	930	0.54	0.04				2,280	2.33	1.84
55. Granulocytopenia (*neutropenia, agranulocytosis)				930	0.32	0.03				753	1.46	0.38
56. Thrombocytopenia (*thrombocytopenic purpura)				3,097	0.03	0.01				892	0.22	0.07
57. Thrombosis of vein												
58. *Hepatic Damage*—Hepatitis (*hepatitis, ascites)				9,869	1.70	0.87	60	0	0			
59. *Local Reactions* (thrombophlebitis, soreness, necrosis, slough, transient pain)	189	0.01	0.01	3,274	2.29	0.66						
60. Myalgia				58	3.45	0.52						
61. *Neurological Disturbances*							36	0	0			
62. Mental disorders and psychoses (*confusion, disorientation, drunkenness, C.N.S. dist.)				4,874	0.51	0.22				1,890	0.95	0.63
63. Cerebral stimulation (*mental irritation, tenseness, nervousness, insomnia)				37	2.70	0.01				151	6.62	0.35
64. Depression (*drowsiness)							130	1.34	0.07			
65. Neurological disorders				3,097	0.74	0.20						
66. *Auditory Disturbances* (tinnitus, deafness—temporary and permanent, partial and total)	118	0.14	0.04	12,394	8.89	9.75						
67. Encephalopathy (*toxic neuropathy)				4,034	0.05	0.02				511	0	0
68. Peripheral neuritis (*nerve palsy, nerve root pain)				72	1.39	0.01						
69. Paresthesia (*numbness—fingers, legs, toes, hyperesthesia)	20	0.05	0.01	7,041	3.30	2.05				151	0.66	0.04
70. Vertigo	293	0.03	0.02		**					151	0.66	0.04
71. Vestibular disturbances (*eighth nerve damage, ataxia)	56	0.04	0.01	10,193	31.81	28.26						
72. *Oral Disturbances*												
73. Stomatitis				210	0.95	0.02	189	1.59	0.10	31	3.23	0.94
74. Glossitis				210	1.43	0.03	468	1.71	0.26			
75. Cheilosis												
76. Tongue discoloration							263	1.52	0.13			
77. Metallic taste												
78. Bitter taste												
79. *Respiratory Disturbances* (*dyspnea, breathlessness, respiratory failure)												
80. Pharyngitis							196	2.55	0.16			
81. *Skin Reactions*												
82. Dermatitis												
83. Desquamative and exfoliative dermatitis	14	0.07	0.01	1,002	0.10	0.09						
84. Dermatitis venenata				59	5.09	0.03	24	4.17	0.03			
85. Photosensitivity												
86. Vulvovaginitis and vaginitis							615	2.93	0.59			
87. Rash (*scarlatino, fleeting erythema)	98	0.04	0.01	6,157	6.43	3.50	312	3.53	0.36	2,153	2.69	2.02
88. *Urinary System Disturbances*												
89. Bladder irritation (*burning urination)												

II—CONT'D

SULFADIAZINE 15,852			SULFAGUANIDINE 3,955			SULFANILAMIDE 14,573			SULFAPYRIDINE 10,484			SULFASUXIDINE 1,230			SULFATHIAZOLE 12,863		
A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
1,037	0.29	0.02	44	0	0	300	0.33	0.01	862	0.35	0.03				1,387	0.22	0.02
741	0.41	0.02															
11,107	1.64	1.15	605	0.17	0.03	10,553	0.52	0.38	6,601	2.12	1.34	28	0	0	12,935	0.70	0.71
6,628	0.02	0.01	15	0	0	11,116	0.23	0.17	3,543	0.79	0.27				2,387	0.36	0.06
						1,114	0.10	0.01							271	0	0
2,506	0	0				3,303	0.52	0.12	2,302	0.26	0.06				3,258	0.09	0.02
									80	1.25	0.01						
100	15.00	0.10				245	1.62	0.03	450	17.33	0.74				399	0.51	0.02
100	3.00	0.20				1,729	1.74	0.21	806	4.72	0.36				52	1.92	0.01
380	0.53	0.01				2,825	0.60	0.12	100	5.00	0.05				271	0	0
141	2.84	0.03															
1,513	0.33	0.03				1,658	0	0	1,164	0.86	0.10				984	0.10	0.01
						6,170	2.80	0.50	108	0	0				5,237	0.04	0.02
1,858	0.38	0.04				7,895	3.80	2.06	778	16.71	1.24	50	2.00	0.08	5,617	2.51	1.10
						6,070	0.08	0.03									
6,070	0.03	0.01							5,037	0.04	0.02						
						6,070	0.89	0.37									
10,145	1.57	1.00				4,691	1.66	0.54	5,510	2.09	1.10				5,807	4.31	1.94
						106	0	0							110	0.91	0.01
10,607	1.18	0.79	1,163	2.67	0.78	11,908	2.26	1.85	3,222	3.85	1.18				2,484	4.79	0.93

TABLE II—CONTINUED

TOTAL NUMBER CASES SYMPTOMS•	DIHYDRO-STREPTO-MYCIN 462			STREPTOMYCIN 11,305			TERRAMYCIN 3,033			SULFAMER-AZINE 2,875		
	A	B	C	A	B	C	A	B	C	A	B	C
90. Kidney disturbances (*renal impairment, nephritis, urinary disturbances, nephrotoxicity)	41	0.02	0.01				153	0	0	585	2.05	0.42
91. Decreased urinary function (*elevated N.P.N., nitrogen retention, azotemia, oliguria decreased P.S.P.)				10,891	4.20	4.04				238	0.42	0.04
92. Albuminuria (*cylindruria urinary casts)	42	0	0	5,754	22.70	11.55	7	14.25	0.03	135	0.74	0.04
93. Nephrosis												
94. Renal calculi (*kidney stones, renal colic, renal obstruction, crystalluria)				131	17.56	0.20				1,582	7.78	4.28
95. Anuria										497	0.40	0.07
96. Hematuria	21	0	0	3,944	4.13	1.44	7	14.25	0.03	88	0	0
97. Hematuria—microscopic										1,558	6.35	3.44
98. Hematuria—gross										1,550	1.23	0.66
99. Renal pain (*loin pain, backache, costovertebral pain)										1,025	0.78	0.28
Reference Numbers				139-154			347 357	363 367	456- 489	204-220		

Key:

A, Number of patients studied for the specific reaction.

B, Percentage of patients studied for the specific reaction, who manifested these reactions.

C, Percentage of the total number of patients receiving the antibacterial agent, who manifested the specific reactions.

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168. Ann. Int. Med. **17**: 920, 1942.
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194. Lancet **2**: 69, 1943.
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201. J. A. M. A. **123**: 624, 1943.
202. J. A. M. A. **128**: 1152, 1945.
203. Gastroenterology **4**: 4, 1945.

II—CONT'D

SULFADIAZINE 15,852			SULFAGUANIDINE 3,955			SULFANILAMIDE 14,573			SULFAPYRIDINE 10,484			SULFASUXIDINE 1,230			SULFATHIAZOLE 12,863		
A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
7,503	1.45	0.69	843	0.12	0.03	811	0.12	0.01	169	0	0				1,293	1.01	0.10
2,212	0.63	0.09	191	0.52	0.03	347	1.73	0.04	5,203	2.04	1.01	177	0	0	796	3.64	0.23
			520	0	0	106	1.89	0.01									
503	0.60	0.02													2,459	0.48	0.09
2,400	4.04	0.06	1,738	31.30	13.76	33	0	0	2,929	2.12	0.59	461	0.43	0.16	5,434	2.01	0.85
1,465	0	0				1,000	0	0	756	1.06	0.08				371	0.54	0.02
2,270	1.81	0.26	761	0.53	0.10	1,553	0.58	0.06	6,524	3.94	2.45	511	0.39	0.16	4,445	5.74	1.98
9,217	2.82	1.64							1,780	2.64	0.45				1,162	5.51	0.50
1,640	1.59	0.16							1,499	1.67	0.24				1,139	0.35	0.03
1,260	2.70	0.21	191	1.05	0.05				490	2.25	0.11						
155-184			185-203			221-241			242-284			285-304			305-346		

*Including.

†Following treatment of spirochetal diseases only.

•When one investigator reported 2 or more reactions which were grouped together in this article under one symptom, only the largest figure was included.

**For streptomycin all reports of vertigo were included under vestibular disturbances.

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231. J. A. M. A. **112**: 115, 1939.
232. J. A. M. A. **115**: 364, 1940.
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235. Ven. Dis. Inform. **20**: 33, 1939.
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gantrisin, Ilotycin, Magnamycin, neomycin, and polymixin B. Only those reports were reviewed which specifically recorded the incidence of toxic reactions to antibacterial therapy.

Owing to the varied manner in which clinicians have recorded and interpreted toxicity and side reactions, the true incidence of a given toxic reaction

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probably lies somewhere between the two percentage figures in columns B and C in Tables I and II. The percentage in column B, usually a higher one, represents a compilation of reported percentage reactions. The percentage in column C has been obtained by dividing the total number of reactions by the total number of cases reported for that drug in this study. The figures at the

389. Gastroenterology **19**: 320, 1951.
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bottom of the column for each drug in Tables I and II refer to the bibliographic reference numbers for that drug.

Some of the reactions listed (particularly those in which only a very small percentage of the total patients receiving a drug manifested such a reaction) could have occurred coincidentally. Thus, association of symptoms with a particular antibacterial agent does not necessarily denote causation.

It is unfortunate that this study could not be based exclusively on investigations directed specifically and exclusively at observations of the toxic reactions to drug therapy. Such worth-while researches have been performed[4-6] in some areas of the investigation of drug action, but seemingly only rarely.

These figures are presented solely as an extensive comparative survey of the literature. It is not possible to draw conclusions or discuss the findings within the confines of this article.

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ASTHMA: CLASSIFICATION OF CAUSES

A Recommended Classification and a Critical Review

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ASTHMA is not a disease. It is a syndrome in which wheezing is the diagnostic feature. By the same token, any syndrome which is characterized by wheezing should be called asthma, particularly if wheezing is accompanied by dyspnea.

Asthma is not a definitive diagnosis any more than colitis, meningitis, pneumonia, jaundice, and congestive heart failure are complete diagnoses. All are syndromes which need further classification to meet the requirements of the American Medical Association's *Standard Nomenclature of Diseases and Operations*,[1] e.g., colitis, ulcerative; meningitis, meningococcic; jaundice, catarrhal.

Attacks of asthma and of congestive heart failure can be relieved by symptomatic remedies, which are somewhat standardized; but long-range management is necessary in both conditions. And, in both, success in treatment requires search for, and recognition of, the mechanisms responsible for the wheezing or the heart failure. Similar comparisons can be made with other syndromes.

Wheezing is usually attributed to narrowing of the airways by edema of the walls, spasm of the smooth muscle, increased secretion in the lumina, and by mechanical obstruction. Such narrowing of the airways can be caused by or accentuated by a variety of mechanisms.

The first part of this report consists of a classification of the types of causes of wheezing together with a discussion of the clinical criteria by which these types of causes may be recognized.

The second part is devoted to a discussion of the rather confusing literature on the classification of asthma plus some suggestions for resolving and avoiding existing and future confusion.

In this report four things are to be emphasized. First, the causes of wheezing are numerous. Second, the recognition of these causes is simplified by classifying them. Third, a reasonably accurate classification can be obtained, usually, by history and physical examination. Fourth, most asthmatics have asthma from multiple causes.

When the history and physical examination are inadequate to classify the causes of the wheezing, x-ray of the chest and sinuses, clinical laboratory studies, evaluation of lung function, bronchograms, bronchoscopy, rhinological

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examination, and psychiatric interviews may be necessary. Skin testing, the procedure which sets the allergist apart from his fellow physicians, is helpful only in the detection of atopic (allergic) causes of wheezing. The recognition of all other causes requires the intelligent application of the diagnostic disciplines of internal medicine.

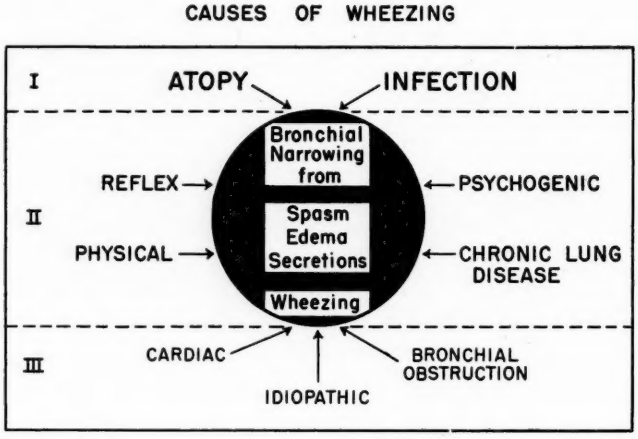

Fig. 1.

The causes of wheezing are classified in Fig. 1. Note that they are in three groups. Atopy and infection, the major causes in most cases of asthma, are in the first group. The second group of causes are: reflex, physical, psychogenic, and chronic lung disease. These factors are more likely to aggravate asthma from atopy and/or infection than they are to be primary causes of asthma. The frequency of troublesome asthma is often determined in any patient by the capacity of this group to exacerbate mild subclinical asthma to clinical levels. In an appreciable percentage of cases, they seem to be the dominant etiological factors. One or more Group II causes are usually present in chronic asthma. In Group III are asthma from left ventricular failure and from bronchial obstruction, which in individual attacks may be indistinguishable from those due to atopy or infection.

Recognition of these causes of asthma usually results from a high index of suspicion and appropriate examinations, outlined below.

Idiopathic causes, which are not susceptible to further classification, should perhaps be put in a fourth group. Discussion of this challenging and important segment of the asthma problem does not seem appropriate here.

The clinical approach to the recognition and classification of these causes of wheezing will be presented in sufficient detail, it is hoped, to be used successfully by the physician not yet initiated into the "mysteries of allergy."

This approach to the study of asthma has evolved from the detailed study of more than 5,000 asthmatics in the University of Virginia Allergy Clinic.

By the application of these simple criteria, our medical students and interns classify the majority of their first cases of asthma with considerable accuracy.

GROUP I. ATOPIC AND INFECTIOUS ASTHMA

Most asthma is due to atopy or infection or a mixture of the two. When atopy and infection are controlled, the secondary causes of wheezing listed in Group II usually become unimportant.

Atopic (allergic) asthma is the familiar type. It is usually due to foods and inhalants, occasionally to drugs. The clinical characteristics of atopic asthma differ strikingly from those of infectious asthma. The more important differences were described in 1922 by Larson and Bell.[2] Brown[3] added to them later. The outstanding features of atopic and infectious asthma are contrasted in Table I. Most of the differential criteria are simple and obvious. Several of them should be emphasized, however. For example, cough is negligible early in the

TABLE I. COMPARISON OF CLINICAL CHARACTERISTICS OF ATOPIC AND INFECTIOUS ASTHMA[6]

ATOPY	DIFFERENTIAL POINT	INFECTION
	HISTORY	
Usually positive	Family history	±
Predictable	Season	Cold and changeable
Late	Cough	Prominent, early
No residual	Cough	Residual
Mucoid, early or late	Sputum	Late, purulent
Mucoid, early or late	Nasal discharge	Late, purulent
Abrupt	Onset of attacks	Gradual
Foods and inhalants	Precipitating factors	Respiratory infection
Frequent	Other allergy	Infrequent
Frequent	Sneezing	Infrequent
Frequent	Itching eyes	Infrequent
Frequent	Lacrimation	Infrequent
Absent	Fever	Common
No effect	Chemotherapy	Shortens or aborts
Good	Response to Adrenalin and aminophylline	Fair or poor
	PHYSICAL EXAMINATION	
Pale translucent swelling	Nasal mucosa	Red, opaque, swollen
Mucoid	Nasal secretions	Purulent
Pale translucent	Uvula	Red, wrinkled
Pale	Tonsils	Red
Pale	Lateral pharynx	Red streaks
Asthma	Chest	Asthma
Transilluminate	Sinuses	Often opaque
	LABORATORY DATA	
Clear or thick mm. symmetrical	Sinus x-rays	Opaque—hazy, often unilateral
Normal	Leukocytes	Elevated or normal
Infrequent	Eosinophilia	Common
Shift to right or normal	Weltmann reaction	Shift to left
Foods and inhalants prominent	Skin tests	Foods and inhalants not prominent

attack. It heralds the end of the attack which comes soon after coughing up quantities of mucoid sputum. The atopic asthmatic coughs himself out of an attack. It is common knowledge that hay fever, urticaria, angioneurotic edema, and atopic eczema are often present in the atopic asthmatic. Other members of his family usually have atopic syndromes. As a rule, the atopic asthmatic knows

that certain foods and inhalants will cause nasal symptoms, cough, or wheezing. He knows also that he has fewer attacks if he avoids those known causes. The rapidity with which he recovers his well-being after he stops wheezing is striking.

On inspection, pale swelling of the nasal and pharyngeal membranes is typical and well known. The pale translucent uvula, which is quite diagnostic, has not been sufficiently emphasized. The immediate type of wheal and flare skin reactions to multiple food and inhalant allergens are the rule. Epinephrine in small doses produces prompt relief usually. Antibacterial therapy has no effect on atopic asthma. It is important to remember that, even now, methods for the detection of asthmagenic foods, inhalants, and drugs are far from perfect.

Infectious asthma in pure form is less common than atopic asthma. The clinical features of infectious asthma are as striking as are those of the atopic type. They are compared in Table I. Cough is diagnostically different. Instead of coming late it usually precedes the attack. The infectious asthmatic coughs himself into the attack. It not only precedes but is prominent throughout the attack and usually persists for a significant time after relief, which follows the production of purulent, thick sputum. Not infrequently cough is as annoying as the wheezy dyspnea.

The nasal and pharyngeal membranes are redder than normal, instead of being pale as in the atopic type. In addition, pus is usually present in the nose or in the nasopharynx. The anterior nasal sinuses often transilluminate unequally. Again the uvula has diagnostic importance which has been little emphasized. In infectious asthma, it is likely to be red, swollen, and wrinkled. Systemic evidences of infection are usually present during, but are absent between, troublesome exacerbations.

Appropriate antibiotics abort or shorten exacerbations of infectious asthma dramatically. In preantibiotic days infectious asthma tended to last for weeks or months. True status asthmaticus is rarely observed in this clinic in the absence of infection. Epinephrine and aminophylline are likely to produce incomplete and transient relief when the attacks are even moderately severe.

In this clinic eosinophilia, 8 to 15 per cent, is considered typical of infectious asthma. Eosinophilia over 5 per cent is seldom seen in atopic asthma here.

Mixed Atopic and Infectious Asthma.—Evidences of both atopy and infection can be found in chronic asthma more often than atopy or infection alone. The history of events preceding the first recognized wheezing usually determines whether the asthma was initially atopic or infectious. This is important because infection complicating atopy seems to be more easily controlled and is seen more often than atopy complicating infection.

GROUP II. CAUSES OF WHEEZING

Reflex, physical, psychogenic, and chronic lung disease may be the dominant causes of asthma. But, usually, one or more are present to accentuate asthma from atopy and/or infection.

Reflex asthma is suggested more often by physical examination than by history. Nasal polyps are the most important reflex causes of asthma. They

are thought to narrow bronchi through the nasal-pulmonary reflex.[4] Relief of chronic asthma by the removal of polyps, lasting until polyps recur, is common.

Thyroid nodules cause reflex asthma occasionally. Sometimes in these cases, finger pressure on the nodule will bring on an attack. Other examples of reflex asthma are the contralateral wheezing commonly seen in carcinoma of the lung and after aspiration of foreign bodies. These causes of reflex asthma should be suspected when there is the history of foreign body aspiration, hemoptysis, weight loss, pain in the chest, unilateral subjective preponderance of dyspnea, or when auscultation discloses unilateral inspiratory stridor or suppression of breath sounds. Other causes of bronchial obstruction present similar diagnostic leads.

The mechanisms which cause reflex asthma, other than the nasal pulmonary reflex, have not been studied.

Physical Allergy.—The role of physical allergy is suspected in any patient who attributes his symptoms to exposures to heat or cold, temperature changes, drafts, wet feet, exercise in cold or in hot air, hot baths, cold baths, or abnormal humidity. The suspicion is confirmed if wheezing can be produced in a symptom-free period by exposure to the physical factors mentioned in the history, or by exposing the hands to hot and cold water and the chest and face to infra-red heat and a tray of ice cubes.

Some idea of the importance of physical factors can be gotten from one group of 104 cases of asthma, 72 of whom attributed their wheezing to physical influences and 27 to foods. One hundred thirty-six inhalants were blamed. In another group of 110 cases, 81 thought physical factors caused wheezing. In 153 simple physical allergy tests wheezing or cough was produced 50 times, other symptoms 100 times.

Physical allergy seems to increase the severity and frequency of attacks of asthma due primarily to other causes. It is rarely the chief cause of asthma. As a rule reactions to physical influences become negligible when atopy and infection are controlled.

Chronic Lung Disease.—Wheezing is frequent in chronic lung diseases such as emphysema, fibrosis, and lung cysts. Dyspnea, cough, and sputum are as typical of the chronic lung diseases as they are of asthma. Wheezing is not always present in the chronic lung diseases. If it is absent, the differential diagnosis offers no problem. When wheezing is present, it is necessary to determine: (a) whether chronic lung disease is present; and (b) how much of the morbidity is due to asthma and how much to the chronic lung disease. Asthma from atopy or infection or other causes can complicate chronic lung disease. Conversely, emphysema and fibrosis are complications of asthma. Thus, there may be a vicious circle in which asthma aggravates the lung disease and the lung disease aggravates the asthma. To provide maximum relief, it is obviously necessary that both the asthma and the chronic lung disease be studied and treated.

Some rather simple observations are usually all that is necessary to recognize chronic lung disease. For example, chronic lung disease is strongly suggested by (a) the history of: dyspnea without wheezing, dyspnea only on

exertion, a long history of cough or exposure to pulmonary irritants, and prompt relief of dyspnea by rest, particularly by lying down (this differentiates cardiac and asthmatic from pulmonary dyspnea); (b) physical signs of: poor respiratory motions of the chest on inspection, the use of accessory muscles of respiration without wheezing, increased anteroposterior diameter of the chest in emphysema, low diaphragm with limited motion, decreased area of cardiac dullness, faint heart sounds, faint breath sounds with prolongation of expiration, prominent systolic thrust in the epigastrium, and venules along the diaphragm attachment.

When the history and physical examination suggest pulmonary disease, it can be confirmed easily by x-ray evidence of bronchiectasis, emphysema, fibrosis, poor diaphragmatic motion, and, occasionally, mediastinal shifting with respiration. The lung disease can be further identified and differentiated by pulmonary function studies. A simple one is the use of a vital capacity apparatus. In chronic pulmonary disease, the total vital capacity may not be significantly lowered at first, but the ability to blow out a significant portion of the total vital capacity at the first expiratory puff is definitely reduced. To be diagnostic, these procedures must be carried out when there is no wheezing, even on auscultation during forced expiration.

Recognition of chronic lung disease is of comparable importance to recognition of heart disease. Control of infection, bronchospasm, and edema of the bronchi and the avoidance of inhaled irritants are often followed by striking improvement in chronic lung disease. Improvement after stopping smoking is often dramatic.

Psychogenic Asthma.—There can be little doubt that the psyche plays an important role in the asthma syndrome. The role varies from time to time in the same patient and from patient to patient. Unfortunately, no satisfactory attempt has been made to evaluate the relative role of psychogenic versus other causes of wheezing. The relative role of the psyche in asthma will continue to be controversial until hundreds of improved cases have been studied comprehensively enough to evaluate the roles of all the listed causes of wheezing. Psychogenic influences seem to play the dominant role in some cases and to supplement atopy, infection, etc., in others.

That the psyche does play a role is attested to by the many reports of chronic asthma relieved only after adjustments are made to "life situations." A simple example of the role of acute emotions in respiratory function is the sniffling and coughing which drown the dialogue in melodramatic movies. Again, anything which threatens the vital function of breathing causes some anxiety. Anxiety causes hyperventilation, which in turn accentuates asthma. There is a variable element of anxiety in every attack of asthma.

Sixteen of seventy-one patients with sinus disease and asthma[5] failed to improve after prolonged conservative and/or surgical treatment of the sinus infection and atopic factors. Nine of these had severe emotional problems obviously related to their symptoms. Criteria for the recognition of psychogenic asthma are similar to those by which other psychosomatic syndromes are recognized.

Psychogenic material in the asthmatic may be detected easily or with great difficulty, depending on the nature of the material. The role of psychogenic influences may be suspected by exclusion of other causes of wheezing or by positive behavior patterns during the history and physical examination.

The following clinical features should make the physician suspect psychogenic wheezing in any patient: (a) The history: irrelevant verbosity; difficulty in obtaining direct replies to direct questions; different replies to the same questions repeated at intervals; apparent satisfaction from the failure of previous treatment; sighing respiration or the history of air hunger between attacks; disclosure, by probing, of a "life situation"; attitudes of depression, involution, anxiety; unconvincing food, inhalant, physical, and infection histories; or any of the common psychosomatic syndromes. (b) Physical examination: dyspnea out of proportion to auscultatory signs of asthma; unnecessary physical exertion in breathing; rapid respiration; panicky behavior; "chain-smoking" of the nebulizer; sighing respiration, clammy hands, and wide pupils between attacks; display by parents of overprotection or rejection during the history, physical examination, or skin tests. (c) Miscellaneous: relief from placebos; poor relief of relatively mild attacks from Adrenalin, ephedrine, and aminophylline; striking relief from sedation with or without atropine.

The role of the psyche in asthma lies somewhere between the views of the fadists who feel that most asthma is psychogenic and the reactionaries who feel that the psyche plays no or an insignificant role.

GROUP III. CAUSES OF WHEEZING: CARDIAC ASTHMA, BRONCHIAL OBSTRUCTION, IDIOPATHIC

Cardiac Asthma.—Paroxysmal nocturnal orthopnea should not be called cardiac asthma unless there is wheezing, which on auscultation sounds like the wheezing due to infection or atopy. Cardiac asthma does not occur in the absence of a form of heart disease which imposes a load on the left ventricle. Conversely, any heart disease which leads to acute left ventricular failure may precipitate true cardiac asthma.

It is seldom possible to diagnose cardiac asthma with certainty during the observation of a part of one attack. The best the physician can do during one attack is to suspect cardiac asthma by observing several of the following strongly suggestive criteria:

(a) The history: known heart disease with a left ventricular load; the proper age for coronary insufficiency; an extreme sense of suffocation or fear of death during an attack; frothy or pink sputum; air hunger sufficient to go to the window or outdoors during an attack; asthma which, after being mild for years, becomes more severe at night with little or no change in daytime attacks.

(b) Physical examination: signs of left ventricular loads; appreciable tachycardia, before medication; greater elevation of the blood pressure during than between attacks; rapid development of cyanosis; drenching sweats during attacks; accentuation of the pulmonic second sound; prompt relief by oxygen, particularly if given by positive pressure; relief from tourniquets or venesec-

tion; fetal or gallop cardiac rhythm; prolonged circulation time during an attack, normal between attacks; x-ray evidence of hilar pulmonary congestion during, but not between, attacks.

When a number of these criteria point to cardiac asthma, it can be proved by treating the patient as though he had congestive heart failure, i.e., by digitalization, salt restriction, diuretics, sleeping in the upright position, marked restriction of activities. No other treatment should be given except to relieve the attacks. If this regime does not stop the attacks of asthma within two or three days, it is unlikely that the patient has cardiac asthma.

A good deal of misinformation has been published about cardiac asthma. For example:

(a) Relief by morphine does not differentiate.

(b) Adrenalin is not contraindicated in cardiac asthma. It usually relieves promptly and effectively; and in small doses it does not increase the blood pressure nor speed the pulse.

(c) Cardiac symptoms may be absent between attacks of asthma. Therefore the absence of anginal pain, or dyspnea, or palpitation on exertion does not rule out cardiac asthma.

(d) Asthma and heart disease may occur concurrently, apparently without aggravation of either by the other.[7] Therefore, the mere presence of heart disease does not mean that the asthma is cardiac asthma.

(e) Paroxysmal orthopnea without wheezing is not cardiac asthma but is properly called paroxysmal orthopnea. True cardiac asthma is more likely to occur in allergic persons.[7] The converse has not been studied.

(f) In an occasional case, evidence of heart disease may be absent entirely by x-ray, electrocardiogram, history, blood pressure, and physical examinations. Cardiac asthma may be present for months before definite objective evidence of impaired left ventricular function can be detected.

(g) Absence of symptoms or signs of congestive failure do not rule out cardiac asthma. The development of congestive failure in a patient with cardiac asthma is likely to bring temporary relief of asthma, because the failing right ventricle cannot pump more blood into the pulmonary circulation than the left ventricle can take out of it.

It is proper to repeat that, when the patient is first seen and perhaps during several attacks, one can only suspect cardiac asthma. It is not proved until treatment of heart failure brings relief of asthma.

Bronchial Obstruction.—Bronchial airways may be narrowed by other means than the spasm, edema, and increased secretion shown in the diagram. For example, bronchi may be narrowed by foreign bodies, polyps, adenomata or cancer; by kinks from contracting scars or expanding cysts; and by external pressure from mediastinal or peribronchial masses.

Wheezing is a common sign of bronchial obstruction, though not an invariable one. Wheezing occurs in two forms: (1) in reflex attacks of diffuse asthma, already discussed, and (2) localized to the area of the obstruction between attacks.

Bronchial obstruction should always be suspected, and necessary diagnostic steps should be instituted to rule it in or out, whenever there is wheezing plus (a) the history of: foreign body aspiration, hemoptysis, unilateral pain in the chest, rapid debility, subjective unilateral air hunger or wheezing, exhausting cough, pulmonary tuberculosis, or other chronic lung infections; (b) physical signs of: localized inspiratory stridor, particularly if present on several examinations, unequal ventilation of the two lungs or of corresponding lobes, visible venous collaterals, orthopnea or cyanosis between attacks of wheezing, enlargement of peripheral glands or spleen.

Wheezing with bronchial obstruction is usually incidental. Attention should be centered on the obstruction and not on the asthma.

Table II lists the chief criteria which should make the physician suspect the presence of Group II and Group III causes of wheezing.

TABLE II. CRITERIA FOR SUSPECTING NONATOPIC, NONINFECTIOUS CAUSES OF ASTHMA

HISTORY OF:	
Dyspnea without wheezing	Relief by
Interval air hunger	Rest
Unilateral emphasis	Supine
Fear of death	Aspiration
Known heart disease	Hemoptysis
Rapidly developing	Chest pain
Debility	Attacks due to
Emphysema	Heat
Exhausting cough	Cold
Seeking air for relief	Weather
PHYSICAL FINDINGS	
Nasal polyps	Inspiratory stridor
Thyroid nodules	No wheezing in attacks
Venous collaterals	Asymmetrical ventilation
+ A-P diameter	Faint heart sounds
Sighing respiration	L. ventricle loads
Interim cyanosis	Interim reduced
Interim orthopnea	exercise tolerance

DISCUSSION—CLASSIFICATION OF ASTHMA

Arnold Rich in his *Pathogenesis of Tuberculosis* stated: "Be on guard against that air of finality and dogmatism that tends to hang like a miasma about all classifications." No air of finality is applicable to this classification. Dogmatism has been employed freely in this report for the sake of emphasis and brevity.

The classification of asthma is not a new problem. Nearly one hundred years ago Henry Hyde Salter[8] wrote, "The circumstances under which asthma may occur are so various, and the features of different cases so peculiar, and impart to those cases such an individuality, that all writers are tempted with more or less success, to make some classification of its different varieties. I say, with more or less success. I might almost have said, with uniform want of success. The chief cause of their failure is, I believe, a want of a simple reading of nature . . . it seems to me to be a subject in which authors have

done more in the way of reading each others books than scrutinizing their own patients." These remarks are as appropriate today as in 1860, when they were published. Salter then offers (Table III) his own elaborate classification. It becomes a remarkable tribute to his powers of clinical observation, when it is realized that there was no knowledge of anaphylaxis, bacteriology, or x-rays; and that there was only meager knowledge of cardiology, otolaryngology, biochemistry, physiology, pathology and pharmacology, or even auscultation.

TABLE III. SALTER'S CLASSIFICATION OF ASTHMA

ASTHMA	Idiopathic, uncomplicated, or spasmodic asthma	1. Exciting cause manifest	Intrinsic asthma, i.e., irritant applied to the lungs themselves	I. Asthma from fog, smoke, fumes of various kinds II. Ipecacuana asthma III. Hay asthma IV. Asthma from animal emanations V. Asthma from certain airs VI. Toxhaemic asthma
			Excito-motory, or reflex asthma	I. Peptic asthma II. Asthma from organic nervous irritation III. Asthma from peripheral cerebro-spinal irritation
			Central asthma; epileptic, emotional, &c	
		2. No apparent exciting cause of attacks; periodic asthma		
	Symptomatic, complicated, or organic asthma	Organic cause vascular	I. Asthma complicating bronchitis, common humid asthma—senile asthma II. Cardiac asthma	
		Organic cause nervous. Heberden's case, &c		

A review of the subsequent literature of the classification of asthma leads inevitably to confusion. For example, it is hard to see how a student could reconcile Walker's[9] classification into sensitive and nonsensitive with Rackemann's[10] intrinsic and extrinsic; Cooke's[11] infective and noninfective; Coca, Thommen, and Walzer's[12] immunologic and nonimmunologic; Larson and Bell's[2] sensitivity determined, sensitivity not determined but history typical of sensitivity cases, chronic bronchitis, cases which did not fit into either of the other groups; Unger's[13] paroxysmal and chronic; Urbach and Gottlieb's[14] allergic and pathergic, Ramirez's[15] allergic exudative and nonallergic spastic. Each of these classifications has multiple and different ramifications.

The literature is further confused by Feinberg,[16] Vaughan and Black,[17] Criep,[18] and others who discuss the classification problem under the headings of "bronchial asthma" and the "differential diagnosis of asthma."

Further confusion arises from the different concepts of intrinsic asthma expressed by Rackemann,[19] Vaughan and Black,[17] Derbes and Englehardt,[20] Cohen,[21] and Alexander.[22, 23]

Finally, sources of confusion are found even in the same books. For example, Abramson[24] states, "All wheezing is asthma although not necessarily allergic," while Forman[24] in the same book states, ". . . difficult to determine

whether a given difficulty with breathing accompanied by some wheezing, is bronchial asthma or some condition for which it is mistaken." Similarly, Cooke[11] classifies asthma as infective, noninfective and cardiac, while Baldwin,[11] in the same book, discusses "Typical bronchial asthma, asthma with structural changes in the heart, lungs and other organs; and those who do not have asthma but have other conditions which may simulate it."

A careful analysis of these seemingly conflicting reports discloses no serious differences in concept. The confusion arises chiefly from differences in terminology. There is also a lack of agreement as to whether the term asthma should be applied to all wheezing conditions or should be limited to "bronchial asthma," which then must be differentiated from other conditions which cause wheezing. The classification which is the basis for this report is the result of an effort to resolve these differences.

The term "bronchial asthma" is redundant. No other structure wheezes. There is no general agreement as to just what "bronchial asthma" is. Multiple types of causes of wheezing are the rule in chronic asthma. The frequency and severity of attacks of asthma are often determined by nonallergic factors. It seems logical, therefore, to discard the word bronchial and to use "asthma" to describe all syndromes in which there is wheezing.

The diagnosis of asthma would be clarified and standardized if, in the *Standard Nomenclature of Diseases and Operations*,[1] it be specified that the term "asthma" be further qualified by listing all of the recognized types of causes of wheezing in each case being diagnosed. Examples are: asthma, atopic (or allergic); asthma, infectious; asthma, atopic, physical, and cardiac; asthma, atopic, infectious, reflex, with emphysema or bronchiectasis, or bronchial obstruction; etc. This diagnostic system has been in use successfully in the Allergy Clinic of the University of Virginia Hospital for many years.

The classification into "extrinsic" and "intrinsic" asthma is probably the most widely known and practiced one. It is recommended that this classification be discarded. Since it is so firmly entrenched, good reasons must be offered to persuade those who use the "extrinsic and intrinsic" classification to substitute another.

Good reasons for discontinuing the classification of asthma into "extrinsic" and "intrinsic" are:

1. The clinical features of extrinsic and intrinsic asthma as described by Rackemann[19] and Alexander[22] concur commonly in the same patient.

2. In the discussions of intrinsic asthma a variety of unrelated causes of wheezing are lumped. And no criteria have been outlined by which these concurrent unrelated causes of wheezing can be recognized and evaluated and treated individually.

3. Intrinsic asthma means different things to different authors. The sections on asthma by Rackemann[19] in Cecil and Loeb's textbook of medicine and by Alexander[22] in Harrison's textbook of medicine and the article by Cohen[21] illustrate this point. Cohen[21] states, "Most of the deaths in asthma

attacks occur in this intrinsic group, in my opinion it is this group which is responsible for the high rate of death after 40 years, which is recorded in the experiences of the insurance companies. . . . Intrinsic asthma might be called 'asthma gravis.' Once the condition is well established there is a gradual downward course in a typical case, and death may occur in from a few months to several years." Note that Cohen[21] referred to intrinsic asthma as "a condition." Whereas Rackemann and associates[25] included under intrinsic asthma bacterial allergy, depletion (with four subheadings), polypoid sinusitis, emphysema, tumors, and foreign bodies, certainly intrinsic asthma attributed to psychofatigue, infected teeth, malnutrition, foreign bodies, tumors (benign) by Rackemann[19, 25] does not belong in the same classification as Cohen's[21] intrinsic "asthma gravis."

4. This identification of intrinsic asthma with a poor prognosis by Cohen[21] and by Alexander[23] should, alone, be sufficient reason to discontinue the use of the term intrinsic, particularly when other authors (e.g., Rackemann) do not imply a poor prognosis when they use the term.

5. Tuft,[26] who objects to the term intrinsic asthma, states: "The mere fact that the patient happens to be past 40 years of age is no valid reason for assuming that he has so-called infectious or intrinsic form of asthma. *Nevertheless, this impression has influenced so many practitioners, that when the middle aged or senile patient complains of asthma, especially of only a few years standing, the ailment is classified almost immediately, either consciously or unconsciously as infectious* [*or intrinsic*]. The tendency to develop or show specific sensitivity to inhalant allergens and particularly to foods is not a faculty reserved only for the young."

6. Rackemann[10, 19, 25, 27-30] has been the most prolific and effective proponent of the extrinsic-intrinsic classification. It seems proper therefore to examine his theses in some detail.

What does he mean by, and how does one recognize, extrinsic and intrinsic asthma? He summarizes his ideas in Table IV.[25]

What is there to criticize in his theses? Several things. For example:

1. Specific criteria are not given by which the clinical impact of the subclassifications can be recognized. Without specific criteria for classification, it is no wonder that different physicians mean different things when they use the term intrinsic asthma.

2. He has emphasized the importance of age as a criterion for classification. For example, "This type of asthma (intrinsic) occurs in older people with onset usually after 40."[25] Again, "A good rule is to remember that when asthma begins before the age of 30, that is allergy (extrinsic) unless proved otherwise; but when it begins after the age of 40, that is not allergy unless proved otherwise."[28]

That these slogans should not be accepted at face value is the contention of Kern[31] who disagrees as follows: "A frequent and serious source of diagnostic error, therefore, is the assumption that asthma beginning after the age of 40 is rarely due to external allergens, but is 'intrinsic,' infectious, non-

allergic. Yet the patient whose asthma began at 70 may have had an allergic rhinitis for 50 years due to the same allergens that now have found an additional shock organ. In my experience, a majority of cases of so-called 'intrinsic' asthma have been shown to have an allergic component, proper attention to which was essential for a good therapeutic result."

TABLE IV. A WORKING CLASSIFICATION OF ASTHMA[25]

ASTHMA BEGINS BEFORE AGE 30	ASTHMA BEGINS AFTER AGE 40
"Extrinsic Asthma"	"Intrinsic Asthma"
Simple	Bacterial allergy (hard to prove)
Diagnosis easy by history	"Depletion"
Complicated by	Psycho-fatigue
Infection	Somatic
Depletion	Infection { sinuses, bronchi, teeth, other
"Asthmatic bronchitis"	Malnutrition
Vasomotor rhinitis leads to asthma (often severe)	Polypoid sinusitis
	Emphysema { functional, structural
	Tumors and foreign bodies
	(Note Selye's "Alarm reaction")

3. The strongest indictment comes from an analysis of the data presented by Rackemann[25, 29] to support his slogans on the importance of age in classifying asthma as extrinsic or intrinsic. What do his data show to support the slogan: "When asthma begins before the age of 30, that is allergy (extrinsic) unless proved otherwise"? In his book[29] (page 375) there were 265 intrinsic versus 333 extrinsic cases under 30, a ratio of about 4:5. Since there are almost as many intrinsic as extrinsic cases under 30, there seems little validity in the slogan. In fact, 128 of his intrinsic cases were under the age of 10.

How well do the data support the slogan: "This type of asthma (intrinsic) occurs in older people, with onset usually after 40"?[25] The answer is, "Not at all." His Fig. 1, reproduced here in Fig. 2, shows the incidence of intrinsic asthma by decades. The dotted insert was added to show that he had omitted from his Fig. 1 the 128 cases under 10 given in his book. In his Fig. 2 of the same article[25] there were perhaps 65 cases under the age of 10 which he omitted from his Fig. 1. His Fig. 2 is reproduced here as Fig. 3. With these corrections his Fig. 1 shows about 410 cases over 40 versus about 540 or 475 cases under 40 (depending on whether 128 cases under 10 are counted from his book or 65 from his Fig. 2). In either case *Rackemann's own data show more intrinsic asthma under than over 40,* thus invalidating his slogan.

It is unfortunate that he did not state simply, and correctly, that the data in his book show more intrinsic than extrinsic cases after 40. But the ratio is only about 7 to 2, hardly enough to justify the implied prognostic prejudice against the 22 per cent of extrinsic cases over 40.

Since it is recommended that the "extrinsic and intrinsic" classification be discarded and since the two slogans quoted above have been widely accepted

as criteria for such classification, it seemed important to point out that an analysis of the data shows that the slogans are inaccurate and misleading.

7. A case of intrinsic asthma as a clear-cut syndrome as described by Alexander[23] has never been recognized in this clinic, although it has been looked for assiduously. All cases which, superficially, resembled Alexander's intrinsic asthma[23] have been resolved into several components by the application of the criteria for classification which have been outlined above.

Continued use of the classification "extrinsic and intrinsic" asthma would seem indefensible in the face of the above objections.

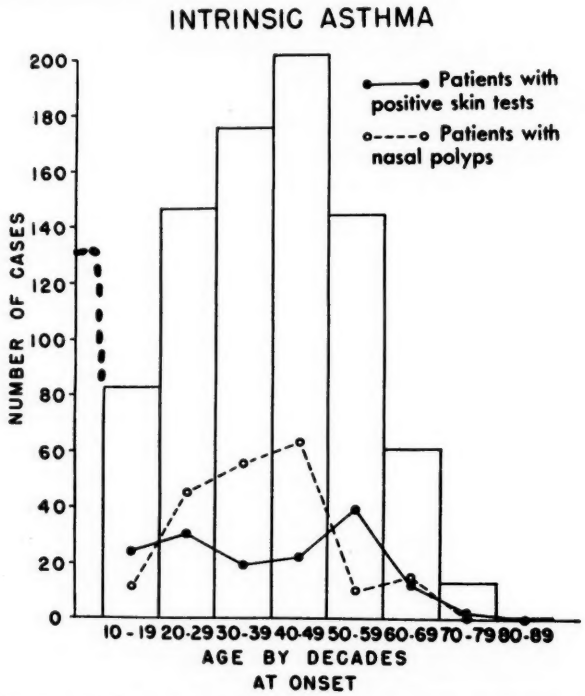

Fig. 2.—Rackemann's[25] data on age by decades at onset of intrinsic asthma. The dotted line has been added to show the 128 cases of intrinsic asthma below the age of 10 shown in Rackemann's book but omitted from his Fig. 1.

The following reasons are offered in support of the recommendation that the classification discussed in this report be substituted for the popular classification of extrinsic and intrinsic asthma and for all other classifications.

The classification discussed in this report is recommended because:

1. Wheezing is due to multiple causes in the majority of chronic asthmatics. In this classification the criteria by which the impact of each of the several types* of causes of wheezing may be recognized are discussed in some detail.

*By a "cause" of wheezing is meant house dust, ragweed, eggs; a nasal polyp; a lung cancer, a foreign body; a draft, a temperature change; maternal rejection; an infected antrum, bronchiectasis; etc.

By "type of cause" of wheezing is meant: atopic; reflex; bronchial obstruction; physical; psychogenic; infectious.

When the type of cause has been identified, it is often necessary to identify the actual cause. Multiple causes within the same type of cause are also common. For example, foods and inhalants as atopic; sinusitis and bronchitis or bronchiectasis as infectious; and bronchiectasis and emphysema as chronic lung diseases are frequent concurrent causes.

2. In the average case, all the types of causes of wheezing can be recognized by the history, physical examination, simple x-ray and laboratory procedures which are available to all physicians.

3. In this classification there are no unlabeled "wastebaskets." In it the small percentage of unclassified cases are properly called idiopathic.

4. This classification avoids the implication of poor prognosis which is widely associated with the term intrinsic asthma and with the onset of asthma in later life. Prognostic criteria should be assembled separately for each case. It so happens that, by applying the criteria for the recognition of the

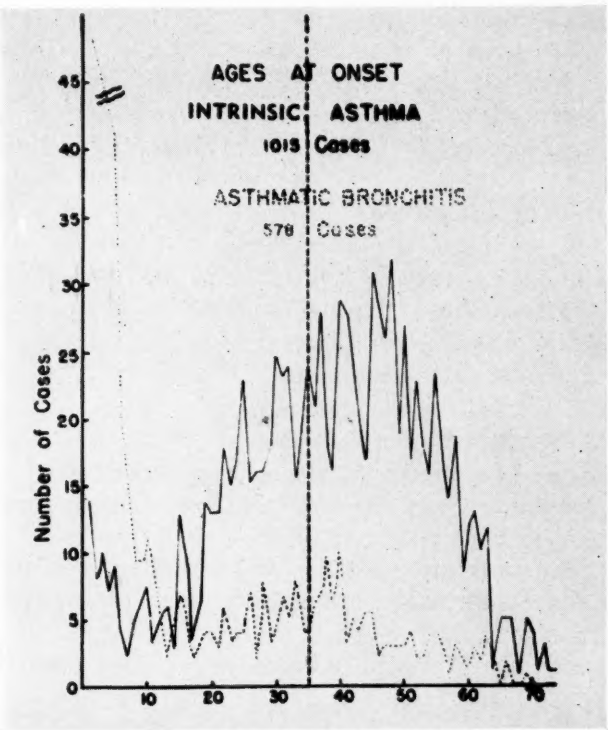

Fig. 3.—About 65 intrinsic cases below the age of 10 were shown in his Fig. 2.[25]

different types of causes of asthma, the physician is confronted automatically with evidences of those complications which influence the prognosis in asthma. The prognosis in uncomplicated asthma is good regardless of age.

5. This classification is not inconsistent with any of the current ones, even intrinsic and extrinsic.

6. This classification recognizes the role of nonimmunologic causes of wheezing without de-emphasizing the importance of the role of allergy. It should be an acceptable compromise to those who have rejected the idea of infectious asthma because allergy to bacteria was the implied mechanism by which infection causes asthma. There is no doubt that many allergic asthmatics get asthma when they get infected and many asthmatics have

asthma only when they are infected. Both examples can be called infectious asthma properly. Whether infectious asthma is due to bacterial allergy, a reflex, or to some other mechanism is not germane to its recognition. This does not in any way lessen the importance of the problem of the mechanism by which infection causes asthma.

7. Any case of chronic asthma is a long-term problem. Therefore, it should be approached by a detailed search for, and an analysis of, all factors which contribute to its persistence. This classification offers a logical approach to such a detailed search and analysis.

SUMMARY

1. Criteria are given by which causes of wheezing can be recognized and classified into: Group I: atopic (allergic) and infectious; Group II: reflex, psychogenic, physical, and chronic lung disease; Group III: cardiac, bronchial obstruction, and idiopathic. Seven reasons are given for adopting this classification.

2. In chronic asthma multiple types of causes are the rule.

3. Skin tests are helpful in the recognition of only one type of cause of wheezing, i.e., atopic (allergic). Other causes are recognized only by the application of the disciplines of internal medicine.

4. The popular classification into extrinsic and intrinsic asthma should be discontinued. Seven reasons are given.

5. Bronchial asthma is a redundant term.

6. Asthma is a syndrome, not a disease.

7. Accuracy and uniformity of diagnosis of asthma would be obtained if the *Standard Nomenclature of Diseases and Operations* required the diagnosis of "asthma" to be qualified by stating all recognized types of causes of wheezing in each case. Examples are: asthma, atopic (allergic); asthma, infectious; asthma, atopic, infectious, reflex; asthma, infectious, cardiac, physical, chronic emphysema.

8. Infection causes asthma. Ignorance of the mechanism by which cause produces effect is a poor reason for ignoring the indisputable fact that infection does cause wheezing.

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HISTAMINE, HORMONES, AND HYPERSENSITIVITY

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THE early description of anaphylaxis and the ensuing efforts made to explain this phenomenon or "lack of protection" gave rise to many theories. It soon became clear that there must be a toxic substance involved, and that this toxin must be released suddenly at the time the second or challenging dose of antigen was administered. Although histamine had been synthesized in 1907,[82] it was not until Dale and his co-workers[12] demonstrated its properties and presented the theory of its release during anaphylactic shock that it was implicated as the toxin involved. It is now clear as a result of much investigation that histamine is indeed released in certain forms of anaphylaxis and can account for many of the symptoms produced. It is to be emphasized, however, that there is a wide variety of hypersensitive mechanisms in which this amine appears to play no active role, although it may be involved in some manner. The intense interest in histamine long overshadowed other approaches to the problem, although the possible role of the endocrines to both hypersensitivity and immunity was considered. As more facts were established, a reasonably close association between hypersensitivity, histamine, and the endocrine glands became increasingly apparent, and this whole problem has been attacked with renewed interest in the past few years.

I. HISTAMINE

Histamine is one of a group of tissue hormones, of which acetylcholine and adenylic acid compounds are prominent members,[21] and all of which have the common property of being powerful vasodilators. It is a normal constituent of body tissues and fluids, being almost ubiquitous in its distribution. The highest concentrations are found in lung, liver, gastrointestinal tract, skin, and mucous membranes. Virtually all histamine is held in the cells in loosely combined form. In this state, it is inactive, and under special circumstances many hundred times the normal quantity may be present without producing active symptoms. A small quantity circulates in the free state in plasma and may also be demonstrated in the cerebrospinal fluid.[30] It is only when histamine is released or passes from the intra- to the extracellular spaces that it is free to exert its characteristic effects. Most of the evidence with reference to anaphylaxis points to the fact that there is no accumulation of histamine as a result of sensitization. Thus the effects produced are due to a shift of pre-existing histamine, and not to its production. As will be seen below, there are circumstances where an actual increase in the amount of histamine may occur, particularly with reference to adrenocortical activity.

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Histamine is derived from foods which contain it and from its precursor the amino acid histidine. The latter is broken down normally by the action of histidine oxidase to urea and water. By the action of histidine decarboxylase, an enzyme which can be demonstrated in splenic tissue,[43] CO_2 is removed, and histamine results. A third source is from the intestine, where histidine is broken down to form histamine by the action of suitable bacteria. As might be expected for such an active substance, potent and rapidly acting inactivators exist. Injected or orally administered histamine disappears, or is rapidly inactivated. Thus Adam[1] has recently shown that only 1% of orally administered histamine may be recovered in the urine of normal man. The intravenous administration of histamine is often accompanied by a fall of the blood histamine of man, presumably due to the activation of some enzyme system.[57] The only mechanism that is understood whereby histamine is destroyed is the enzyme histaminase, first described by Best.[5] Although present in the tissues of animals, in the human it can be demonstrated only in the plasma of pregnant women.[2, 66] Excretion of histamine takes place both via the intestine[48] and kidney.[1] According to Roberts and Adam,[55] urine histamine consists of a small percentage in the free state, and a larger portion which is in the conjugated form. The latter is primarily acetylhistamine.

Although histamine has many pharmacologic properties, since there is scarcely an organ in the body which will not respond to it in some manner, its main actions are to stimulate smooth muscle and glandular secretion, and to increase capillary dilatation and permeability. It will readily be seen that most of the symptoms of anaphylaxis, as well as many of the common forms of allergy, may be accounted for by these properties. Relatively little is known of the physiologic role of histamine, in spite of a great deal of work. It is believed by some to be similar to, if not identical with gastrin because of its well-known capacity to stimulate the secretion of HCl in the stomach. Histamine and adrenalin have opposite actions. The fact that an injection of one leads to a release of the other[76, 77] has led to the postulate that these two compounds act together to control circulation in various regions of the body. The recent observations of Gray and Munson[25] indicate that intravenously injected histamine stimulates a release of ACTH from the anterior pituitary of the rat. It is therefore possible that this may be one of its physiologic properties, although this is by no means certain.

It was originally held that histamine is carried by the eosinophile,[10] and there are still occasional references to this in the literature. Observations on the blood of man have not substantiated this view. Thus, in cases where there is a very high blood eosinophilia, the blood histamine is usually within normal limits, and marked fluctuations in the eosinophiles, whether spontaneous or induced by the administration of ACTH, are unaccompanied by any change in the blood histamine content.[29] On the other hand, it has been shown that the blood histamine is enormously increased in the leukemic states.[59, 80] When a reduction of the immature cells is brought about by an agent such as deep x-ray therapy, there is a parallel fall of the blood histamine

as the cells decrease. Examples of such changes will be found in Tables I and II. Table I shows random samples of blood taken at various intervals in a patient with periarteritis nodosa in which the characteristic fluctuations in the total white count and the marked fluctuations in eosinophiles varied from 11 to 80%. The variations in the blood histamine taken at the same time were within normal limits and bore no relation to the variation in eosinophil

TABLE I. BLOOD HISTAMINE AND EOSINOPHILIA
(Patient E. N. Periarteritis Nodosa)

DATE	R.B.C.	W.B.C.	% LYMPH.	% POLY.	% MONO.	% EOSIN.	TOTAL BLOOD HISTAMINE γ/100 cc.
1945							
Dec. 9	5,400,000	23,000	0	18	0	65	5.0
1946							
Feb. 24	———	——	—	—	-	—	5.0
Feb. 25	5,110,000	6,600	30	39	1	30	—
April 15	4,670,000	9,300	11	71	7	11	—
March 12	———	——	—	—	-	—	5.0
March 26	———	——	—	—	-	—	3.0
March 30	———	——	—	—	-	—	2.2
June 24	5,220,000	22,000	5	15	2	78	5.2
July 8	———	24,000	12	8	-	80	4.2
July 16	———	——	—	—	-	—	5.0
July 18	———	16,700	13	13	0	74	—
July 24	———	17,000	16	19	2	63	3.8

counts. In Table II are blood findings in a patient with myelogenous leukemia prior to deep x-ray and for a period of approximately a month thereafter. It will be seen that practically all of the white cell elements were immature myeloid cells. In this condition the blood histamine is normally markedly elevated and before treatment, with a white count of 555,000, the blood histamine contained 1000 gamma per 100 cc. As the white count decreased following deep x-ray, there was a decrease in the histamine content

TABLE II. BLOOD HISTAMINE IN MYELOGENOUS LEUKEMIA
(Patient: D. T.)

DATE 1947	W.B.C.	% LYMPH.	% MYELO. (TOTAL)	% EOSIN.	% MONO.	BLOOD HISTAMINE γ/100 cc.
April 25	555,000	0	100	0	0	—
April 29	———	-	—	-	-	1,000
April 30	Deep x-ray started					
May 3	———	-	—	-	-	750
May 6	380,000	0	98	2	0	—
May 8	———	-	—	-	-	616
May 10	———	-	—	-	-	475
May 13	———	-	—	-	-	350
May 15	———	-	—	-	-	300
May 17	190,000	1	98	1	1	—
May 20	———	-	—	-	-	220
May 21	133,000	1	99	0	0	—
May 23	109,000	0	98	2	0	160
May 27	78,000	0	99	1	0	120

of the blood which was still markedly elevated by the time the total white count was 78,000. (The blood histamine values in normal individuals vary between 4 and 7 gamma per 100 cc.) Patients with leukemia in whom the blood histamine is usually markedly elevated do not show allergic tendencies. Since the examples in the tables are abnormal cells, it does not follow necessarily that polymorphonuclear leucocytes carry histamine under normal circumstances, but the likelihood exists.

II. HYPERSENSITIVITY IN ANIMALS

The term hypersensitivity has come into use as an all-inclusive one. It may be applied to all forms of anaphylaxis, allergy, and other mechanisms which depend upon the combination of antigen with antibody, the result of which leads to some pathologic alteration. The accepted basis on which all such manifestations depend is the combination of antigen with its specific antibody. Some of these changes are temporary, leaving no recognizable aftereffects. An example is the wheal and flare of urticaria, or the acute asthmatic attack in a young person. Others are slower in onset and leave more permanent damage, such as the lesions of periarteritis, or the Arthus phenomenon. It will be obvious, however, that there are many immune reactions, based on antigen-antibody combination which are apparently protective in nature and which do not lead to damage of host tissue. Examples are the response to bacterial invasion such as occurs in pneumonia or typhoid and upon which specific tests depend. The borderline between immunity and hypersensitivity is vague, and much remains to be clarified as yet. One essential difference between them is that in the former instance it is the tissue of the invading organism which is ultimately inactivated or destroyed, whereas in the latter it is the tissues of the host which are altered. Basically, however, the mechanism is the same.

Any one of the classical forms of anaphylaxis may serve as a basis for discussion. Thus, following the parenteral introduction of a foreign protein into an animal species such as the guinea pig, dog, or rabbit, antibody production is stimulated. The appearance of antibody can be demonstrated most readily in rabbits by the method of simple precipitins, or preferably by the much more accurate technic of Heidelberger and Kabat.[27] While it is reasonably certain that such antibody is in essence gamma globulin,[36] there is some doubt that this is so for the various types of antibody which can be demonstrated in man.[44] The probability is that the latter are either gamma globulin or some closely allied fraction. There is a difference of opinion regarding the actual site of antibody formation, evidence in favor of the reticuloendothelial system,[71] the lymph nodes,[14] and, finally, the plasma cells[6] having been championed by various investigators. Regardless of where antibody is formed, reintroduction of the specific or same antigenic substance into the now sensitized animal leads to a series of events rapidly culminating into what is termed general or tissue anaphylaxis. The injected antigen combines with antibody to form a complex, and there is evidence to show that a proteolytic enzyme system, probably plasmin, is activated.[56] Cell stimula-

tion or, under certain circumstances, actual damage or destruction may occur. In the former case, reversible changes occur accompanied by a release of metabolites such as histamine and heparin. It is this release of histamine which is primarily responsible for the production of symptoms. The variations in symptomatology are due to species differences and distribution of smooth muscle.[60] In this form of classical rapid anaphylactic shock the symptoms may be completely prevented by the previous administration of an antihistamine. Furthermore, in the nonsensitized animal, symptoms virtually indistinguishable from anaphylaxis may be produced by the injection of histamine. And, finally, the release of histamine from tissues both *in vivo* and *in vitro,* by the combination of antigen with antibody, has been amply demonstrated.[60] A simple scheme of these events is shown in Fig. 1. Here, then, the evidence is quite clearly in favor of the histamine theory.

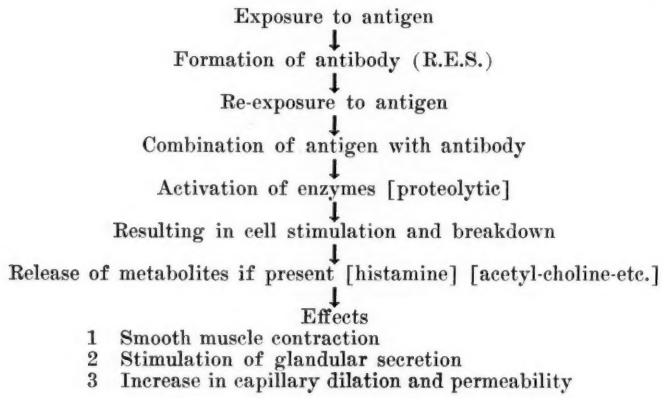
Exposure to antigen
Formation of antibody (R.E.S.)
Re-exposure to antigen
Combination of antigen with antibody
Activation of enzymes [proteolytic]
Resulting in cell stimulation and breakdown
Release of metabolites if present [histamine] [acetyl-choline-etc.]
Effects
1 Smooth muscle contraction
2 Stimulation of glandular secretion
3 Increase in capillary dilation and permeability

Fig. 1.—A simple scheme of the mechanism of anaphylaxis.

In contrast to these common forms of anaphylaxis, there are other forms of hypersensitivity in animals, the lesions of which also are dependent upon combination of antigen with antibody, but where there is little or no evidence in favor of histamine participation. Examples are the Arthus phenomenon in the rabbit, and the delayed form of vascular and tissue change characterized by periarteritis, myocarditis, and the formation of Aschoff-like nodules, as demonstrated by Rich.[53] Many other examples might be added. These syndromes cannot be reproduced by the injection of histamine, nor can they be inhibited by the action of antihistamines.[16]

A general observation might be made here, to the effect that histamine release seems to be related to those rapidly produced, reversible states. These changes are associated primarily with an increase in the permeability of endothelium, and it is the view of Halpern[26] that antihistamines exert their prime effect by decreasing permeability. Other changes of course occur in guinea pig and rabbit anaphylaxis, but it is not these which produce death. This is due to asphyxia in the former and to right-sided heart failure in the latter species.

III. RELATION OF ENDOCRINES

Attempts to establish a relation of the various endocrine glands to hypersensitivity have been numerous. Findings of apparent significance seem to be confined to the gonads, the thyroid, the anterior pituitary, and the adrenal cortex. Of these, the results relative to the adrenal are by far the most important, and of its various steroid components, those of the 11-oxy variety hold most prominence.

Little is known regarding the role of the gonads in hypersensitivity, although symptoms of allergy have so very frequently been described in association with puberty, the menarche, menstruation, pregnancy, and the menopause. There is undoubtedly some connection, but no basic work has been done. It is known, however, that the administration of progesterone to pregnant rabbits will heighten the histaminase activity of the plasma.[3] Recently, Kapeller-Adler[33] has shown that estradiol benzoate, when added to histaminase *in vitro,* increases the activity of this enzyme.

An interesting relationship between thyroid activity and histamine metabolism was demonstrated by Gotzl and Dragstedt,[24] who found that removal of the thyroid gland leads to a decrease in the histamine content of tissues in the rat. Leger *et al.*[37] observed that whereas removal of the thyroid increased the resistance of the rat to the egg-white reaction, administration of while of interest in that they are opposite to those associated with adrenothyroxin rendered the animal much more sensitive. These observations, cortical activity, are limited and require further investigation.

It is with the adrenal cortex, and its regulation by the anterior pituitary that most investigation has been conducted and will be the prime subject of discussion. As pointed out elsewhere, little known relation exists between hypersensitivity and the androgens.[61] The major portion of experimentation has been concerned with ablation of the adrenals or administration of ACE (adrenocortical extract) or more recently cortisone or ACTH.

Early experiments indicated that removal of the pituitary increased the susceptibility of guinea pigs to anaphylaxis,[35] and later that resistance to histamine was impaired by adrenalectomy.[4] In considering the relation of histamine to anaphylaxis, Rose and Browne[63] investigated the role of the adrenal cortex. It was found that the ability of the adrenalectomized rat to inactivate injected histamine was markedly impaired as compared to the intact animal,[64] and that this was due in part to a reduction in the activity of the enzyme histaminase.[34] In addition, an increase in the histamine content of tissues such as stomach, intestine, as well as blood, was demonstrated.[65] These findings were later confirmed by others.[42] It was observed that these changes could be restored only partially by the administration of DOCA, but the injection of adequate amounts of ACE, on the other hand, resulted in restoration to within normal limits, but not greater.

There are other aspects of the hypersensitive state which have been probed in a similar manner. Of these, the relation of antibody production to adrenal cortical activity is of particular interest. It will be seen that contro-

versial results have been reported, depending upon animal species, and the type of antigen used. The early work of Marine and his co-workers[31, 78] indicated that removal of the adrenals in rabbits was followed by an increase in the antibody titers of sensitized animals. In 1947 Murphy and Sturm[47] showed a similar effect in the same species, and this has again been confirmed recently by Criep *et al.*[11] The complementary effect, namely a reduction in the antibody titer of sensitized intact rabbits following the administration of cortisone was shown by Germuth and Ottinger[22] and confirmed by Bjorneboe *et al.*[7] The latter workers[17] showed further that the effect of cortisone was apparently limited to actively produced antibody, for when antibody in the form of plasma from sensitized rabbits was transferred passively, cortisone had no effect. They thus feel that the mode of action whereby cortisone reduces antibody in this species is to suppress antibody formation, rather than by protein breakdown. The state of affairs in the rat is as yet unclear in that the original contention of Dougherty and White[13] that administration of ACE increased antibody formation in the intact animal has not been confirmed.[15, 79] In a recent discussion by Mirick,[45] it was indicated that adrenalectomy in the rat is followed by a reduction of antibody formation, whereas the administration of cortisone to the intact animals induced an increase in the antibody titer. When one considers the findings in man, it becomes apparent that antibody production is either not altered by the administration of ACTH as shown by Herbert and de Vries[28] or it may be slightly enhanced according to Mirick.[45] There can be no question that increased gamma globulin in man, such as is commonly found in lupus erythematosus is consistently lowered by the administration of ACTH or cortisone.[8, 52, 74] Since Mirick was able to show a decrease in gamma globulin without a decrease in the antibody titer, it may be that antibody is not identical with gamma globulin in man, and this further complicates the picture. There is the possibility that certain types of antibody are inhibited by cortisone, whereas others are not. In support of this is the finding that the immediate reacting skin test in allergic patients is not affected, even though the clinical symptoms are completely suppressed. The tuberculin reaction is said to be prevented both in animals[40] as well as in man by the administration of cortisone or ACTH.[41] Both of these skin reactions are dependent on the presence of antibody. It may be, of course, that it is the tissue reaction which is primarily affected, for the tuberculin as well as other reactions due to the injection of bacterial products is inflammatory in nature, whereas the immediate skin reaction is dependent on the release of histamine.

Another important factor is the macrophage system. An illuminating contribution on the relation of adrenocortical activity to the reticuloendothelial system was made by Gordon and Katsh.[23] They showed quite clearly that the uptake of thorium dioxide by the R.E.S. of the liver and spleen was impaired by adrenalectomy and could be restored to normal by the administration of ACE. Recently, however, Spain et al.[75] noted that the ability of the macrophage cells in the peritoneal cavity of mice to take up carbon particles

was impaired by the previous administration of cortisone. It is difficult to compare these experiments because of species difference and the dose of agents used.

Finally, with reference to adrenalectomy in animals, there is the factor of sensitization. Rats and mice, both difficult to sensitize in the intact state, are readily sensitized and precipitated into anaphylaxis following ablation of the adrenals.[18, 46] In confirmation of this, Criep et al.[11] have recently shown that adrenalectomy in rabbits enhances the development of anaphylaxis, the Arthus phenomenon, as well as the production of experimental diffuse arteritis, using the method of Rich and Gregory.[53] According to Selye,[73] periarteritis nodosa-like lesions may be produced in the rat by the administration of massive doses of DOCA. It is difficult to compare this type of arteritis with those just discussed, for, in the former, a sensitizing agent such as horse serum must be used, and the species of choice is the rabbit. Since there is no known immune or hypersensitive mechanism associated with the DOCA form of arteritis, it is unlikely that it is related to those forms common to man since these are for the most part associated with some form of sensitivity as shown by Rich.[54]

IV. ALLERGY

Turning now to the manifestations of hypersensitivity in man, one finds considerably less evidence of a direct nature to support the role of histamine. Thus, whereas histamine release is characteristic of the acute anaphylactic state in animals and can be demonstrated with ease in the blood of the guinea pig or the dog, there is only one condition in man where this can be demonstrated with certainty, and this is in the condition known as hypersensitivity to cold. This syndrome is characterized by swelling of a diffuse urticarial nature on the exposed portions of the body, such as the hands and face, when the patient goes out in cold weather. These are also the subjects who develop sudden syncope on going into cold water. Experimentally, one can demonstrate evidence of a general effect, such as increase in pulse rate, drop of blood pressure, as well as transient but significant increase in the histamine content of the plasma as well as whole blood. An example of these changes following immersion of the hands and forearms in water at 4° C. for five minutes will be found in Fig. 2.

Attempts to demonstrate significant changes in the blood histamine in the common forms of allergy have been largely unsuccessful. It was thought that since rapid and potent inactivators of histamine might conceivably destroy it soon after its release from an organ such as lung, a blood sample taken from the antecubital vein might not reflect the true state of affairs. For this reason, Rose, Rusted, and Fownes[70] catheterized the pulmonary artery and placed an indwelling needle in the femoral artery of a group of asthmatic subjects. No change in the histamine content of the blood sampled from either pulmonary or femoral arteries could be demonstrated either during the quiescent state or during attacks of asthma induced by various means.

In spite of this inability to demonstrate alterations of blood histamine in association with the production or appearance of symptoms, there is much evidence to support the view that histamine metabolism is grossly disturbed in patients with the common forms of allergy.

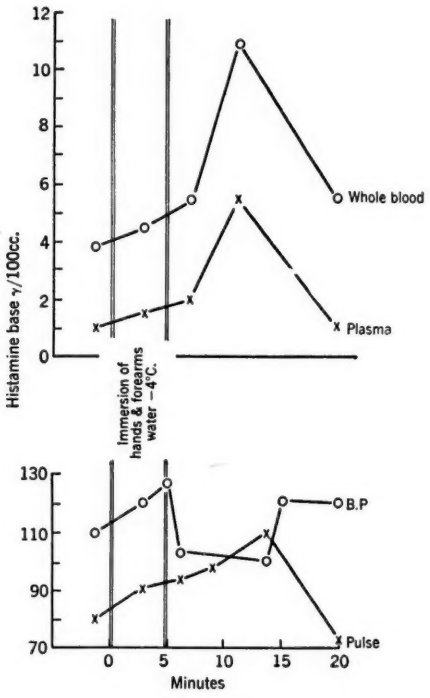

Fig. 2.—The effects of immersion of the hands and forearms in a water bath at 4° C. for five minutes in a patient with sensitivity to cold. It will be seen that the total blood histamine rose from a level of 4 gamma per 100 cc. to 11 gamma at the ten-minute period, and then returned to 5 gamma. The active or free histamine, which normally is present in very small amounts, rose from the control level of 1 to 5 gamma per 100 cc. at the ten-minute period. This release of histamine was associated with a drop in the blood pressure, a rise in the pulse rate, and intense flushing of the face and neck. Swelling and itching of the immersed portions of the forearms began at about 15 minutes and was intense at the 20-minute period. This is one of the few conditions in which a significant release of histamine in association with the production of symptoms can be demonstrated in man.

If one now compares the manifestations of hypersensitivity in man with the adrenalectomized animal, some striking similarities will be found. For example, whereas in the normal subject the blood histamine remains relatively constant over periods of time, marked variations in the histamine content of blood have been observed in patients with eczema or asthma.[58] The values may be many times that of the normal, but these increases are of the total blood. The histamine is intracellular and, therefore, inactive. Of greater significance, perhaps, is the fact that such variations bear no direct relation to the appearance or disappearance of symptoms. Rose *et al.*[69] have also noted that whereas the normal individual excretes from 50 to 500 gamma histamine per 24-hour urine output, as much as 250,000 gamma (250 mg.) histamine per 24-hour urine has been found in some patients with asthma, or eczema, or

both. In a survey of the histamine content of the tissues of man, Rose, Baxter, and Entin[62] found that lung tissue of nonallergic patients varied from 15 to 20 gamma per gram. It was possible to obtain samples of lung from a young patient with asthma whose left lower lobe was removed at operation for bronchiectasis. The values here were 120 and 130 gamma per gram in two separate specimens. There is yet another difference in the behavior of asthmatic patients to histamine, and that is the heightened sensitivity to this substance. Injection of histamine in the normal subject produces the usual excretion of HCl in the stomach, flushing, tachycardia, and, occasionally, a drop in blood pressure. No change in respiration has been recorded. Although by no means universal, a high proportion of asthmatic subjects will respond to injected histamine with a moderate to a brisk attack of asthma which is virtually indistinguishable from a clinical attack. They therefore are more sensitive to histamine than are nonasthmatics.

Histaminase, the enzyme which destroys histamine, may be measured only in the plasma of pregnant women. It begins to appear in the first month, rising steeply until the seventh month and remaining within fixed limits until parturition.[2] Following this, the histaminase activity of the plasma declines rapidly and has usually disappeared by the forty-eighth hour. During pregnancy in the human, it is derived from the placenta, and there is evidence to show that it may be influenced both by estrogens[3] and progesterone.[33] Pregnancy influences many states, including that of hypersensitivity, and it is well recognized that asthma or eczema may disappear with pregnancy, usually at the second or third month. However, in a percentage of cases, not only does pre-existing asthma not disappear, it may be made worse. Studies on the histaminase content of the plasma of normal pregnancies, as well as asthmatics whose symptoms disappeared with the onset of pregnancy, showed normal values throughout.[66] On the other hand, when asthma or eczema failed to disappear or actually came on during pregnancy, the plasma histaminase was below normal.[67] In addition to the alteration in plasma histaminase, a marked increase in the excretion of urine histamine was observed. These findings are similar to those described by Kapeller-Adler[32] for toxemia, and will be referred to again in relation to steroid excretion.

There are several other attributes of the allergic state which seem to fit in with the general concept and which will now be considered. The so-called nonallergic individual, although exposed to all the same environmental antigenic substances (or allergens) does not become sensitive. It is a well-known phenomenon clinically that an individual with an allergic tendency may be sensitized easily to horse serum, as was found in the days of diphtheria antitoxin administration. Furthermore, an individual with pollen asthma in a ragweed-free area soon develops both positive skin tests to ragweed as well as clinical symptoms in the ragweed season after moving to a ragweed infested area. Thus, allergic subjects appear to become sensitized much more readily than nonallergic individuals.

In the young asthmatic, skin-sensitizing antibody is present, and may be readily demonstrated both directly and by passive transfer. This may be

considered as abnormal, since it is not present in normal nonallergic individuals. Another characteristic is the eosinophilia of blood and tissues, as well as a lymphocytosis which is not uncommon. When all these attributes of so-called allergic subjects are compared with the changes that take place in the experimental animal following removal of the adrenals, a considerable similarity between the two will be apparent. These are listed for convenience in Table III.

TABLE III. COMPARISON OF EFFECTS OF ADRENALECTOMY IN ANIMALS AND FINDINGS IN ALLERGY

	ALLERGIC MAN	ADRENALECTOMY ANIMALS
Sensitivity to histamine	Increased (asthma)	Increased
Disturbed histamine metabolism	Yes	Yes
Tissue histamine	Increased	Increased
Urine histamine	Increased	?
Tissue histaminase	?	Decreased
Plasma histaminase	Decreased	?
Antibody production	Increased (Skin sensitizing)	Increased
Eosinophilia	Yes	Yes
R.E.S. activity	Decreased	Decreased
(resistance to infection)	Decreased	Absent
Corticoid excretion	(Intrinsic)	
Ease of sensitization	Increased	Increased

Finally, there is the question of adrenocortical activity itself, and before discussing this aspect of the subject it may be worth while to clarify the two large groups of allergy, according to Rackemann.[50] The young, or "extrinsic," asthmatic has the following attributes. Skin tests are positive, and there is usually a strongly positive family history. The symptoms are almost always precipitated by some external environmental factor such as inhalants of the season (ragweed) or nonseasonal (animal danders or feathers) variety. Eosinophilia is moderate but may be markedly elevated. Between attacks there are normally no signs of disease, with the exception of the positive skin tests. There is little weight loss. As a general rule, the excretion of corticoids is within normal limits, and the response to ACTH is marked by a brisk increase in the excretion of corticoids to well above normal limits. The so-called intrinsic asthmatic is usually older, the onset of symptoms usually occurring about the age of 35 to 45. The symptoms are not usually related to external factors, but more often to infection. The skin tests are usually negative or of little significance, and there are evidences of the disease between acute bouts. Often there is a loss of weight. In this latter group, Venning, Johnson, and Rose[81] found evidence of a lowered adrenocortical activity as measured by the urinary output of both glucogenic and formaldehydogenic corticoids. In these patients the administration of ACTH may increase the urinary corticoids to within the normal limits, but seldom above. It should be pointed out that these two groups of asthma are arbitrary and there is considerable overlapping. While both are considered to be "allergic" in nature, the evidence for this is much stronger in

the case of the younger so-called extrinsic group for obvious reasons. Examples of the excretion of corticoids in one of each type are shown in Figs. 3 and 4. The lowered output of corticoids in this older group of asthmatics may be considered as evidence of an impaired adrenocortical function, although it is recognized that this point will require further elucidation when more accurate methods become available.

If Figs. 3 and 4 are examined, it will be evident that severe asthma and all the "stress" that this condition entails, which is not inconsiderable if it be remembered that these patients may and do die, are apparently insufficient to stimulate the pituitary adrenal mechanism. Yet it is not uncommon to see

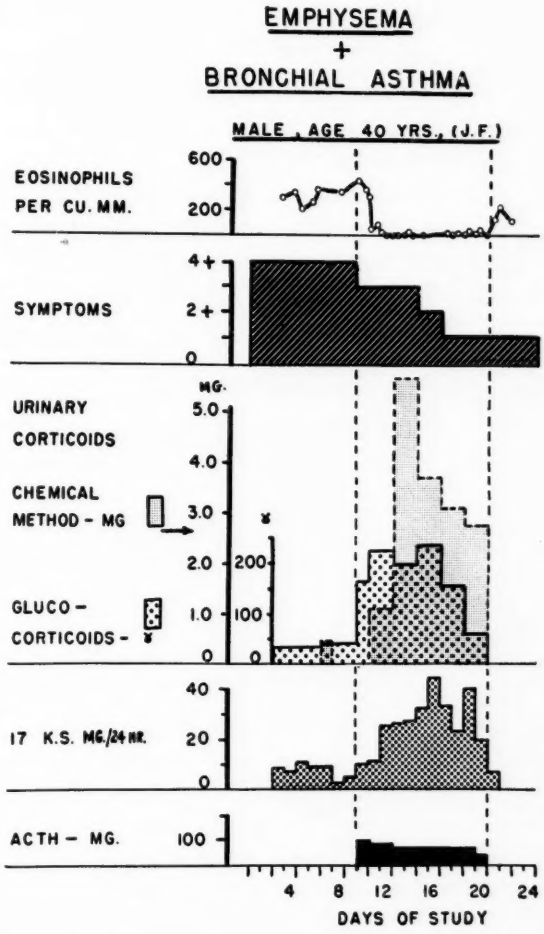

Fig. 3.—This shows the change in the eosinophil count, the symptoms, excretion of both chemical and glucocorticoids in the urine, the excretion of 17-ketosteroids, and the administration of ACTH, from above downwards, in a young male aged 40, with a history of asthma since childhood and markedly positive skin tests. He had a moderate amount of emphysema. It will be observed that during the control period there was no significant increase in the excretion of corticoids or 17-ketosteroids, which were within normal limits. Following the administration of ACTH, there occurred a prompt rise in the glucocorticoids which was well marked. A similar marked increase was observed in the chemical corticoids. The response was evident by a marked increase in the 17-ketosteroids as well.

the disappearance of asthma and a drop in the eosinophilia when some other condition such as strangulated hernia, or surgical interference, or not infrequently a high fever due to some acute infection supervenes. It would appear, therefore, that either the asthmatic state is an insufficient stimulus to the anterior pituitary, or that some block in the pathway leading to the pituitary is characteristic of the condition. It may be that some individuals develop asthma because of the latter possibility, but this is pure conjecture.

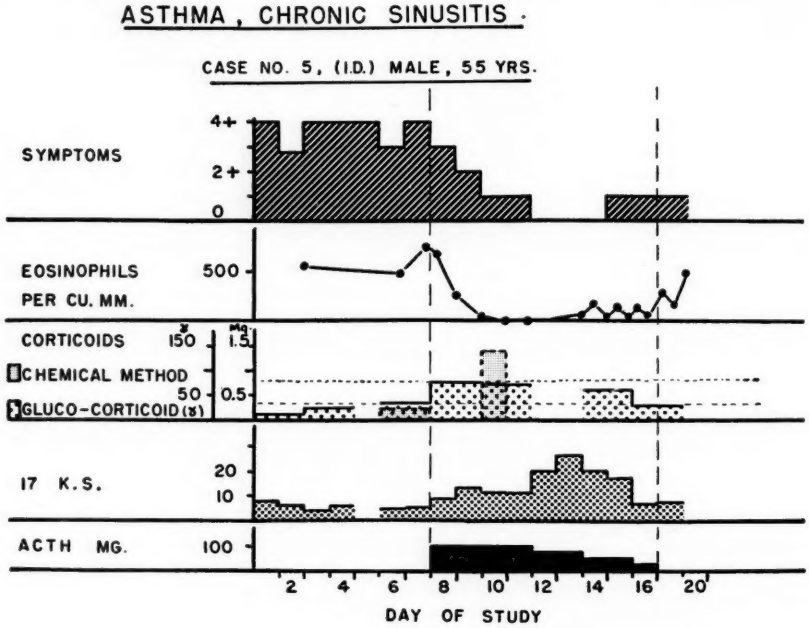

Fig. 4.—This shows the symptoms, eosinophil response, corticoids, 17-ketosteroids, and the administration of ACTH in a male patient aged 55. He was free of trouble until the age of 40, when he developed a chronic sinus and shortly afterwards asthma which has remained related to infection and is worse in the winter months. Skin tests were negative, and there was no history of allergy in the family. In contrast to the findings in Fig. 3, it will be observed that both the glucocorticoids and chemical corticoids are considerably lower during the control period and that, following the administration of ACTH in a comparable dose, there occurred an increase in the glucocorticoids to within normal limits only. This was also reflected in the increase of chemical corticoids. The response of the 17-ketosteroids was not remarkable.

Lest the impression be gained that the foregoing discussion is designed to implicate histamine as a major factor of allergic disease, Table IV, which is a partial comparison of the effects of cortisone and the synthetic antihistamine compounds, is presented. It will readily be seen that there is little in common. Cortisone and ACTH have no effect on guinea pig anaphylaxis.[19, 38] The symptoms are mainly due to histamine release, and it is well established that this can be completely controlled by the administration of antihistamines. Histamine shock in animals behaves in a similar fashion as might be expected.[19] Carryer and Code demonstrated[9] that histamine release in vitro could not be abolished by the presence of cortisone. This indicates that the transfer of histamine from intra- to extracellular spaces by the interaction of antigen with antibody is not prevented by cortisone under

these circumstances. One of the enigmas of ACTH and cortisone therapy in man is that while they are able to abolish the clinical symptoms of asthma in the extrinsic forms, the skin tests are not altered.[39, 68] It is reasonably well established that the wheal and flare which characterize the so-called immediate reacting type of skin test which is produced by the intradermal injection of protein extracts and is read in 15 minutes are due in part to local histamine release. The wheal and flare are usually on the wane within an hour and are temporary. Antihistamines markedly and often completely suppress this reaction.[16]

TABLE IV. COMPARISON OF EFFECT OF ANTIHISTAMINES AND CORTISONE

	ANTIHISTAMINE	CORTISONE
Anaphylaxis (guinea pig)	+++	—
Resistance to histamine	++++	—
Immediate reacting skin tests (man)	+++	—
Hay fever	+++	+±(?)
Serum reactions drug eruptions	+++	+++
Arthus phenomenon	—	+++ (Indirectly by suppressing antibody)
Delayed type skin tests (T.B.) (man)	—	+±
Asthma rhinitis (VMR)	±	+++
Periarteritis, lupus, etc.	—	+++
Tissue anaphylaxis (animals)	+±	++++
Egg-white phenomenon	+++	+++
Globulin	—	+++ (Man) (Rabbit)

On the other hand, the delayed form of skin test, typified by the tuberculin test, which takes about 48 hours to become positive, is unaffected by antihistamines, but may be reduced or even prevented by ACTH or cortisone.[40, 41] This reaction, primarily vascular in nature, is characterized by tissue alteration and damage, and may even go on to local necrosis.

Studies on the effect of ACTH or cortisone in seasonal hay fever are relatively few and controversial.[20, 39] This is one of the few forms of clinical allergy where antihistamines seem to be efficacious.[16] There is no question, however, that the antihistamines are virtually useless as treatment in the vast majority of cases of asthma, particularly the severe ones.[16] Here ACTH and cortisone have found their greatest clinical application, particularly in the intrinsic forms.[61]

Periarteritis nodosa, both experimentally produced and in its clinical form, may be ameliorated by ACTH or cortisone, whereas the antihistamines are without effect. Again, this latter is to be expected since there is no evidence to support histamine as an active participant in the production of symptoms. The group of collagen diseases as a whole may be considered in the same category.

One of the few phenomena which appear to be equally prevented by cortisone or the antihistamines is the egg-white reaction in rats, described by Selye.[72] This reaction is due to a natural hypersensitivity to egg white, since

only a single injection is required to produce the symptoms, consisting of edema of the snout and paws. The underlying mechanism is not understood.

These findings therefore would seem to indicate that although histamine metabolism is profoundly altered by adrenocortical activity, the relation is one which seems to deal with storage and general metabolic effects, whereas cortisone appears to have little effect on the rapid and often explosive release phenomenon associated with anaphylaxis or skin tests. Even after all clinical symptoms have been suppressed by cortisone or ACTH administration, those phenomena due to histamine release, such as the positive skin tests in man, or the effects of injected histamine remain unaltered. One possible conclusion from such evidence therefore is that the more common forms of allergy, such as asthma, rhinitis, and eczema, while associated with an altered metabolism of histamine, are not in themselves dependent on histamine release as such. It would also seem logical to suppose that since the skin-sensitizing antibody in allergic man is unaltered by cortisone administration, it may not enter into the active production of symptoms, although this must still remain an assumption.

In spite of the fact that the guinea pig has been regarded as the counterpart of human allergy in animal species, only the mouse appears to be protected against acute anaphylaxis by the previous administration of cortisone, as recently shown by Nelson *et al.*[49] It would seem, therefore, that in considering further approaches to acute reversible hypersensitivity, and the delayed forms resulting in the collagen diseases, rats and mice are preferable for the former, and the rabbit for the latter. The mechanism of the therapeutic use of ACTH and cortisone in man, which has been considered extensively elsewhere,[61] still remains enigmatic.

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DISCUSSION

A. S. Gordon.—I wish to thank Dr. Rose for the kind remark he made concerning the work of Dr. Katsh and myself which has dealt with the relation of the adrenal cortex to the macrophagic cell system. He mentioned also that some other results have not been in total agreement with ours. He was probably referring to the experiments of Spain, Molomut, and Haber in which cortisone was administered to normal mice and a reduction in macrophagic cell response to carbon particles was noted. I should like to point out that their mice were given amounts of cortisone which are probably not physiologic and which resulted in overdosage phenomena of various types. A comparable dose in a 250-g. rat, for example, would be 20 mg. daily. In all our work we have made use of adrenalectomized and hypophysectomized rats, and whole adrenal cortical extract has been employed as the sole replacement therapy. We are still of the opinion that more normal physiology is to be learned from a study of the effects of the whole extract than from the artefacts of cortisone overdosage. We concur with the idea that crystalline cortical steroids in high dosages will depress the macrophagic cell system, as they do many other tissues in the body, but we have not found this to be the case with physiological quantities of the whole cortical extract administered to the animal lacking adrenals.

I. F. Somerville.—I would like to make two points relevant to the interpretation of the data presented by Dr. Rose. First urinary steroid levels may be profoundly influenced by changes in the intermediary metabolism of the hormones and, secondly, steroids may influence histamine metabolism. That neither of these possibilities is entirely improbable in the present connection is suggested by the demonstration of abnormal metabolism of administered steroid in at least one syndrome, rheumatoid arthritis (Somerville, Marrian, Duthie, and Sinclair, 1950) and of the influence of administered steroids on circulating histaminase (Kapeller-Adler, 1951).

B. Rose.—There are two hormones which are known to influence histaminase apart from the adrenal steroids of the 11-oxy type. These are estrogens, as shown by Kapeller-Adler, and first referred to by Dr. Somerville, and progesterone, which stimulates production (Ahlmark). I have deliberately left out these findings because of lack of time. With reference to the first point raised by Dr. Somerville, I quite agree that there is a strong possibility of abnormal steroids playing a role in some forms of allergy.

J. Loraine.—I should like to make one comment with reference to Dr. Kapeller-Adler's work. We performed a number of studies in Dr. Gaddum's laboratory in cases of pre-eclamptic toxemia in which the urinary excretion and serum concentration of chorionic gonadotrophin were estimated, using the prostate weight method of assay. In a few

patients Dr. Adler made concurrent estimates of serum histaminase activity employing her chemical method. There appeared to be a definite reverse relationship between the C.G. levels on the one hand and the serum histaminase on the other. High urinary and serum titers of C.G. were encountered in approximately 30% of the pre-eclamptic patients and were much more frequent in severe pre-eclamptics than in moderate or mild cases. Dr. Kapeller-Adler has shown that severe pre-eclampsia is often associated with a low serum histaminase activity.

R. Hertz.—We have studied the urinary histidine by microbiological determinations in some fifteen patients with cervical carcinoma. We have given 250 mg. of progesterone daily, from fifteen to fifty days, and we have found in no case an increase in urinary histidine. In some cases there was a suggestive decrease indicating that the histidinuria of pregnancy is not attributable to progesterone per se. In addition in our breast cancer patients treated very intensively with very high doses of estrogens, stilbestrol by mouth, as much as 30 mg. daily continuously over several months' time, histidinuria also did not occur. Now that suggests that we might rule estrogen or progesterone as the basis for the histidinuria of pregnancy. That leaves the chorionic gonadotrophin as the possible endocrine basis for this unusual metabolic event, and to investigate it we have studied the urinary histidine in four cases of hydatidiform mole, two cases of chorioepithelioma of the uterus, two cases of chorioepithelioma of the testis. In all these the urinary gonadotrophins were very markedly elevated way above the normal pregnancy level, and in none of these cases did we see a histidinuria. We are hopeful that perhaps that differential point may allow for a differential diagnostic test between normal pregnancy and chorioepithelioma or hydatidiform mole.

P. L. Munson.—I should like to hear Dr. Rose's comments on the low sensitivity of the rat to histamine.

B. Rose.—That's a very interesting question, but I do not know the answer.

F. Gudernatsch.—Dr. Rose made the distinction between two groups of individuals, viz., "normal" individuals, in whom the histamine titer remains fairly uniform over the years, and the second type, prone to develop allergic reactions sooner or later, in whom the titer shows steadily recurring fluctuations, sometimes of considerable extent. In this connection I should like to bring up the following questions: Within the allergic group there are two subgroups of different ages. One comprises children in the first decade of life who develop multiple allergies, often very severe ones, including asthma, but who "outgrow" (as the term goes) their affliction or, at least, fail to show further clinical manifestations as they approach and pass through puberty. What is known about changes in the histamine titer or in the physiological efficiency of the suprarenal cortex in such young individuals?

On the other hand, there is the large number of patients who first begin to show allergic manifestations, hay fever, asthma, etc., in the fifth decade of life or later (a condition which often has been claimed to arise on an inheritance basis). Again, are there in these older individuals any demonstrable changes at that time in the histamine titer or in the activity of the cortex?

B. Rose.—I cannot answer this question directly. There are, however, certain observations which appear to be pertinent. We have found that the young children with asthma or eczema usually show a fluctuating blood histamine level which is much higher than that found in older asthmatics. We have also found that in this younger group, the excretion of urinary corticoids is usually within normal limits and responds briskly to ACTH. When such children or young adults lose their symptoms or "outgrow" the disease, it is probable that some endocrine factor plays a role, but the nature of this is unknown. It is of interest in this connection that when such an occurrence takes place, the skin tests may remain positive. Again, in two siblings of an allergic family, one with active symp-

toms and the other without, it is not uncommon to find skin tests positive in both. This is again of interest in view of the fact that whereas ACTH or cortisone controls symptoms, the skin tests remain unaffected.

Of the older, so-called intrinsic asthmatics, it is felt that there is more evidence in favor of an impaired adrenocortical activity because of the lowered output of steroids and other factors mentioned previously this morning.

G. Sayers.—I have a question in connection with the evidence for a relative state of adrenocortical insufficiency in individuals with asthma. It is interesting that the stress of the disease itself apparently does not cause an increase in adrenal cortical activity, yet surgical trauma and other types of stress will. I am wondering if you would like to speculate as to which component of the pituitary adrenocortical system is involved. It is apparently a situation in which a single specific stress will not bring about stimulation of the adrenal cortex. I would like to ask you if there is any evidence for metabolic changes in asthma compatible with adrenocortical insufficiency. I am thinking particularly of electrolyte and carobohydrate metabolism. Is there any evidence from metabolic studies that adrenocortical insufficiency exists in individuals with asthma?

B. Rose.—With reference to the first question, the evidence for impairment of adrenal cortical function is based on the studies, part of which I showed this morning, namely the fact that these individuals have a lowered output of glucocorticoids both by the chemical and biologic method, as well as the fact that they have an eosinophilia, although I am sure that is not the only criterion of impaired activity of the adrenal cortex either. The other findings, namely those in reference to histamine metabolism, do fit in in some measure with those that are found following the removal of the adrenals in the rat and in the rabbit. These are the increase in histamine in the tissues in both the rat and those found in allergic individuals and the variations in the blood histamine, as well as the enormous amounts that appear in the urine. That doesn't necessarily mean to say that because these changes in histamine metabolism are present, that the clinical change must be allergic. It does, however, point to the fact that there is a similarity between adrenalectomy in the experimental animal and the individual with severe asthma primarily and to a lesser extent other forms of allergy.

With reference to the second question that Dr. Sayers asked, we have studied some twenty-five patients by balance methods, including electrolytes, doing nitrogen balance, vitamin C, and so forth, along with those studied by Dr. Browne and Dr. Johnson. In these the only abnormality which we could find which made these patients differ from others was the abnormal amount of histamine which appeared in the urine. Even though we found the odd case of rheumatoid arthritis with a histaminuria, it has never been to the same level as the phenomenal amounts appearing in cases of eczema and asthma. I cannot answer Dr. Sayer's other query, as to which component of the pituitary adrenal system is involved in surgical trauma. There is evidence that this is via a pathway in the cord as shown by Hume. Just why asthma, which is one of the most stressful of all conditions and from which young people may die, fails to stimulate the pituitary is a very interesting question. One possible answer, of course, is that asthma persists or even comes on in the "intrinsic" form just for that very reason. That, so far as we are aware, plus of course the abnormal eosinophilia which can be enormously elevated again is a differentiating point.

A. Albert.—Is anything known about the histaminase level of the blood in patients with Addison's disease who become pregnant?

B. Rose.—Some time ago I had a controversy when asked about the occurrence of allergy in Addison's disease as I had never seen any cases of asthma in a true Addisonian. But I am told that it does occur in a much more fulminating way than it does in the ordinary individual with intact adrenals. As to the level of histaminase in Addisonians becoming pregnant, I have never had an opportunity of examining an Addisonian during pregnancy, and I don't know of any studies that have been done under these circumstances.

P. H. Forsham.—In analyzing a series of some two hundred patients with Addison's disease for asthma and various other allergic manifestations, including food allergies, an incidence of 10% was noticed. This would appear to be somewhat higher than the incidence of similar diseases in the normal population, but not significantly so. One of fifteen patients with hypertension subjected to bilateral adrenalectomy, who had been suffering from mild hay fever previously, developed a very severe type of hay fever and associated asthma following removal of the adrenals. This isolated finding fits in with the results obtained following acute adrenalectomy in animals.

Dr. Rose's clear-cut demonstration that neither cortisone nor ACTH had any effect on histamine in urticaria recalled Dr. Dougherty's talk of yesterday. His crucial test for compound F-like activity consisted of the inhibition of a typical cellular reaction to small amounts of histamine. This apparent inconsistency might be explained, however, when we recall that Dr. Dougherty mentioned specifically that endothelial changes were not inhibited by compound F or cortisone. Since the formation of a wheal depends on vascular leakage conditioned by endothelial changes, the ineffectiveness of ACTH and cortisone mentioned by Dr. Rose in the presence of urticaria due to histamine-like substances finds a ready explanation.

I should like to ask Dr. Rose if there is anything known about the histaminase content of eosinophiles?

B. Rose.—The answer to the last question, as far as I am aware, Dr. Forsham, is no. If anybody has done any work on the histaminase content of eosinophiles I would like to know how he isolates the eosinophiles.

J. W. Jailer.—I was going to answer Dr. Albert's question, but Dr. Forsham has beat me to it. In our experience we have seen allergies of various sorts in Addisonians, but the incidence of allergic phenomena is no higher than in normal individuals. We have had one Addisonian who demonstrated a sensitivity to ACTH which was manifested by fever and urticaria. This happened to be the first incidence of an urticarial reaction we had ever seen with ACTH, and therefore we were very excited about it. However, she also reacted similarly to penicillin.

Addisonians may become pregnant and do very well, especially after the first trimester. We have done nothing in the way of histaminase levels. There is good evidence that the placenta contains an adrenal-like steroid.

B. Rose.—I'd like to make just one comment with reference to urticaria with ACTH, because in a series of some twenty patients with various types of urticaria we have found that about four of this group respond to either cortisone or ACTH whereas the rest don't respond in any way whatsoever.

R. G. Hoskins.—Dr. Francis Rackemann is the authority for the statement that 50% or more of clinical allergy is psychogenic. I wonder if Dr. Rose would care to have discussion of this situation complicated any further by the consideration and would indicate his thinking along that line? Also, it is the common impression among psychiatrists that allergy is much less frequent among schizophrenic men than other persons. Would Dr. Rose care to comment on that too?

B. Rose.—Dr. Hoskins, these are two very interesting comments. The first one puts me in a very difficult position because I am surrounded by psychiatrists. I hold a view that is somewhat as follows. If a person has asthma, there are undoubtedly emotional disturbances or situations which could precipitate an asthmatic attack, and therefore one can say that in part this is psychogenic in origin. I do not believe such a thing to be possible in someone who hasn't the necessary factors in his makeup, such as the tendency to develop sensitivities or other allergic manifestations. Once the latter has been established, then emotional factors may aggravate existing symptoms.

With reference to the second question, I am at a complete loss. I know of a case which was described to me by Dr. Charles Walton of Winnipeg. This woman was a severe

asthmatic in hospital. During the course of her illness, she developed a psychosis, and promptly lost her asthma. She was therefore transferred to a psychiatrist who, being a conscientious man, promptly treated her with electro-shock therapy. This cured her of the psychosis, and her asthma promptly returned. I find this difficult to explain.

R. G. Hoskins.—I know of two other patients who are free from asthma when psychotic, but resume their asthma when the psychosis waves.

F. Gudernatsch.—Mr. Chairman, I do not know whether a question on methods of therapy is in order in this discussion. If so, I should like to ask Dr. Rose the following question in reference to Ménière's disease which clinical syndrome happened to be listed on the first slide shown by Dr. Rose a propos of his remarks on histamine titer.

Dr. Rose informed me just now that in individuals afflicted with Ménière's disease there appear to exist no significant deviations from the average histamine level in the normal.

There is a school of allergists who hold increased liberation of histamine into the bloodstream responsible for the exacerbations in the clinical manifestations of Ménière's and who advocate histamine injections as an efficient therapeutic measure, presumably for desensitization. Other experts in this field violently oppose such a measure.

Would Dr. Rose be willing to express an opinion as to the rationale of the histamine method of therapy? I should also appreciate his opinion as to the use of other transient vasodilators, for instance nicotinic acid derivatives, in the above condition.

B. Rose.—Undoubtedly, some cases of Ménière's syndrome do get better when they are desensitized, so-called, to histamine either by the subcutaneous or intravenous route. There is much speculation regarding the role of histamine in this syndrome. Sometimes attacks may be precipitated by the administration of a large dose of histamine, and some investigators believe that liberation of histamine is the precipitating cause.

Editorial

LATE EFFECTS OF CORTISONE AND CORTICOTROPIN

SEVERAL years of increasingly wide use have established beyond doubt that cortisone and corticotropin have pronounced therapeutic effects in the alleviation of allergic symptoms. While it is apparent that these benefits are transitory and in no sense alter the underlying state of hypersensitivity or lessen the need for specific treatment in the long-term handling of chronic or recurrent allergic disease, their efficacy so far exceeds that of other available nonspecific agents that they will continue to be commonly employed in the symptomatic relief of these conditions. Furthermore, they offer at least palliation to those patients chronically disabled by severe intractable asthma which has resisted the best possible efforts at specific allergic diagnosis and therapy.

Valuable as they are, the use of these agents imposes a serious responsibility on the attending physician to be thoroughly familiar with and alert in detecting their undesirable side effects. Nothing could better exemplify the truisms that we must treat patients not symptoms and that no amount of highly technical knowledge can make a good specialist of one who is not first a good doctor.

The therapeutic effects of cortisone and corticotropin in allergic diseases do not result from correcting a hormonal deficiency, but rather from creating an artificial state of hyperadrenalism in which the supply of cortical hormones is several times the normal requirement. The presence of this excess may be expected in time to produce the known physiologic and anatomic effects of hyperactivity of the adrenal cortex. Fortunately, the dosages usually required to control allergic symptoms only occasionally produce serious effects during the first few weeks of treatment.

The early hormonal side effects of salt, water, and sugar metabolism are widely known, easily detected, and reversible except in patients with serious complicating diseases. The possible mental effects are somewhat more serious but also tend to spontaneous recovery when the drug is discontinued.

When prolonged maintenance treatment with cortisone is undertaken the possibility of other serious complications must be recognized. Many of these are insidious in onset and not easily reversible when recognized. For example, the activation of unsuspected latent tuberculosis or peptic ulcer will often prove a more difficult and dangerous problem than the disease for which cortisone was prescribed. Because of lowered resistance, acute infections may reach a serious stage if not promptly and efficiently treated. While some danger of such complications is inevitable, much can be done to reduce their incidence by careful study of the patient before and during treatment.

One of the less known dangers of prolonged cortisone administration was brought out by Irwin and co-workers[1] at the recent meeting of the American

Academy of Allergy, namely, decalcification of the skeleton to a point where collapse of vertebral bodies and pathologic fractures occur. Negative calcium balance has been recognized as a feature of hyperadrenalism; its actual clinical significance in patients under treatment with cortisone has attracted little attention and will require further study. It serves, however, to further emphasize the need for careful observation when the natural hormone balance is deliberately upset for therapeutic purposes.

In the presence of an excess of exogenous cortisone, it is to be expected that the adrenal cortex of the patient remains inactive and inevitably undergoes partial atrophy. Bennett[2] has reported that adrenal glands of persons who have received cortisone for more than five days and in total doses of more than 450 mg. show definite changes, which persist for a variable period from three to as long as six or more weeks, after treatment is discontinued. The anatomic changes suggest that the adrenal cortex would be unable to function during periods of stress, and confirmation of their actual clinical importance is supplied by several instances of postoperative death, apparently due to acute adrenal cortical insufficiency, in patients who had received cortisone treatment and whose adrenal glands showed typical atrophic changes.[3, 4] It is recommended that when a surgical operation becomes necessary in a patient who has received cortisone treatment, that additional dosages be given intramuscularly. After operation the most careful observation is essential, with prompt and vigorous treatment at the first signs of circulatory collapse.[4]

In case of severe acute infection arising during cortisone treatment, the problem is more difficult since the unfavorable effect of cortisone on resistance to infection must be weighed against the risk of acute cortical insufficiency. The balance of evidence indicates that in the presence of severe infection it is unwise to stop cortisone abruptly and safer to continue it while using appropriate antibiotics.

Recognition of these possible results makes it obvious that prolonged treatment with cortisone is not to be undertaken lightly. It is warranted only in such conditions as severe intractable asthma and periarteritis nodosa, in which the certainty of chronic disability without treatment outweighs the possibility of serious complications arising as a result of it. In chronic asthma, a reasonable degree of relief by a relatively small dose which may require the use of other symptomatic remedies at times probably is generally preferable to an attempt at complete control of symptoms by cortisone only.

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Announcements

The American College of Allergists

The Tenth Annual Congress and Instructional Course of The American College of Allergists will be held at the Roney Plaza Hotel, Miami Beach, Florida, April 5 to 10, 1954.

The first three days will be devoted to the Instructional Course with Dr. Ethan Allan Brown as Chairman and Dr. Hal Davison as Co-chairman, and a group of forty instructors.

During the Postgraduate Course Dr. Hans Selye will be a guest speaker with the subject of "Stress and the Allergic Disorders," also Dr. Alvan Barach will speak on "Recent Advances in Inhalational Therapy of Lung Disorders." There will also be a symposia covering nasal, pulmonary, and dermatologic allergy, steroid hormones, pediatric allergy, psychosomatic allergy, and other interesting features.

The general meeting will be held on Thursday, April 8, Friday, April 9, and Saturday morning April 10. Dr. J. W. Gowan, Professor of Genetics at Iowa State College, will be the guest speaker whose subject will be "Individuality as a Factor in Resistance to Disease." Dr. M. Murray Peshkin will deliver the Presidential Address.

In addition to the "General Sessions" under the Chairmanship of Dr. Giles A. Koelsche, there will be sections on pediatric allergy, otolaryngologic allergy, and dermatologic allergy, as well as round table discussions at luncheon.

Italian Society of Allergy

An extra Meeting of Italian Society of Allergy was held at Florence on June 15, 1953. During this meeting a new board was elected:

Prof. Giovan Battista Belloni (Padova)
Prof. Giovanni Favilli (Bologna)
Prof. Virgilio Chini (Bari)
Prof. Franco Flarer (Padova)
Prof. Piero Di Mattei (Roma)
Prof. Antonio Lunedei (Firenze)
Prof. Marcello Lusena (Milano)
Prof. Flaviano Magrassi (Napoli)
Prof. Guido Melli (Milano)
Prof. Piero Redaelli (Milano)
Prof. Piero Sangiorgi (Milano)
Prof. Umberto Serafini (Roma)

The following officers were elected:

Prof. Cesare Frugoni as Honorary President
Prof. Antonio Lunedei, President
Prof. Guido Melli, and Giuseppe Favilli, Vice-Presidents
Prof. Umberto Serafini, General Secretary

Correspondence to the Director or the Secretary may be addressed to Via Guicciardini n. 2, Florence, Italy.

The official organ of the Italian Society of Allergology, legally constitutionalized, will be published in January of 1954 under a remodeled form with the title of "Folia Allergologica."

The Board of Directors has decided to hold in December of 1954 the second National Congress of Allergology.

Course at University of Pittsburgh

The American College of Physicians will conduct a course at the University of Pittsburgh, School of Medicine in "Diseases Due to Allergy and Immune Mechanisms," for the week beginning with Monday, May 17, 1954. This advanced course will be for physicians already engaged in the practice of allergy. It will consist of didactic presentations, laboratory demonstrations, and panel discussions in which the registrants will participate. All those interested please address your inquiry at your earliest opportunity to Leo H. Criep, M.D., The Bigelow, Bigelow at Tunnel Streets, Pittsburgh 19, Pa.

Request for Correspondence

Dr. Ramon Surinyach, 183 Balmes, Barcelona, Spain, a member of the American Academy of Allergy, would like to correspond with allergists doing research on bronchitis in cotton mill workers. Dr. Surinyach speaks and writes English.

Obituary

ARTHUR FELIX ROCHE was born in Bristol, Conn., on March 3, 1894. He received his early education in the elementary schools of Bristol and later attended Holy Cross and Georgetown Universities. He was graduated with the degree of Doctor of Medicine in 1917 from the Georgetown Medical School. He served his internship at St. Francis Hospital, Hartford, Conn., and Grace Hospital in New Haven, Conn.

He entered military service in World War I as a First Lieutenant in the Medical Corps, was discharged in 1919, and entered the practice of pediatrics in Bristol, Conn.

In 1927 he moved to Hartford and practiced the specialty of Allergy, becoming one of the first to practice this in the state and was soon recognized as an outstanding allergist. His interest in allergy was measured by his many appointments. He was in charge of Allergy at the St. Francis Hospital, Hartford Dispensary, Consultant in Allergy at the Bristol Hospital, and was made a Fellow of the American Academy of Allergy at its inception in 1943.

Dr. Roche was a member of the Connecticut State Medical Society, Hartford County Medical Association, Hartford Medical Society, and the American Medical Association. He was also a member of the American Legion and the Exchange Club of West Hartford.

By his death on April 11, 1953, the Academy has lost an outstanding allergist whose keen insight into the problems of the allergic sufferer will be greatly missed. He is survived by his wife, a son, and a daughter.